

ANESTHESIA & ANALGESIA

Journal of the International Anesthesia Research Society



Ambulatory Anesthesia

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Capnography, Antacids, and Esophageal Ventilation

CO₂ Laser Radiation Reflection From Tracheal Tubes

Nitroprusside- or Nicardipine-Induced Hypotension

For surgical procedures
90 minutes or longer...

ARDUAN

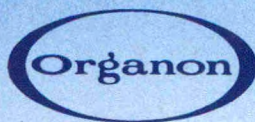
(pipecuronium bromide
for injection

Long-acting muscle relaxation without vagolytic effects¹

- Does not cause elevation of heart rate or blood pressure.²
- Recommended when cardiovascular stability is desired.³
- A useful alternative to pancuronium in patients where tachycardia is best avoided.⁴
- Provides good to excellent intubating conditions within 2.5 to 3.0 minutes.

See following page for brief summary of prescribing information.

P, 24,547



ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

ARDUAN®

(pipecuronium bromide)
for injection

Cub-H0200-43-P02454
02999 -

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: None known.

WARNINGS: ARDUAN® (PIPECURONIUM BROMIDE) FOR INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ARDUAN® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM. In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. Shorter-acting muscle relaxants than ARDUAN® may be more suitable for these patients.

PRECAUTIONS: General: Since ARDUAN® has little or no effect on the heart rate, the drug will not counteract the bradycardia produced by many opioid anesthetic agents or vagal stimulation. Consequently, bradycardia during anesthesia may be more common with ARDUAN® than when a muscle relaxant (such as pancuronium) which exerts vagolytic action is employed.

Renal Failure: ARDUAN®, in the dose of 70 µg/kg actual body weight (ABW), has been studied in a limited number of patients (n=20) undergoing renal transplant surgery recently dialyzed in preparation for cadaver renal transplant. The mean clinical duration (injection to 25% recovery) of 103 minutes was not judged prolonged; however, there was wide individual variation (30 to 267 minutes). ARDUAN® has not otherwise been studied in patients with renal failure (for elective or emergency non-renal surgery). Because it is primarily excreted by the kidney, and because some shorter-acting drugs (vecuronium and atracurium) have a more predictable duration of action in patients with renal dysfunction, ARDUAN® should be used with extra caution in patients with renal failure.

Increased Volume of Distribution: Conditions associated with an increased volume of distribution, eg, slower circulation time in cardiovascular disease, old age, or edematous states, may be associated with a delay in onset time. Because higher doses of ARDUAN® may produce a longer duration of action, the initial dose should not usually be increased in these patients to enhance onset time; instead, more time should be allowed for the drug to achieve maximum effect.

Hepatic Disease: There are no data on dosage requirements, onset, duration, or pharmacokinetics in patients with moderate or severe hepatic dysfunction and/or biliary obstruction. This should be considered in selection of muscle relaxants for use in these patients.

Obesity: The most common patient condition associated with prolonged clinical duration was obesity, defined as 30% or more over ideal body weight (IBW). Clinical study subjects were dosed on the basis of actual body weight, which may have contributed to the higher incidence of prolonged duration. It is therefore recommended that dosage be based upon ideal body weight for height in obese patients.

Malignant Hyperthermia (MH): Human malignant hyperthermia has not been reported with the administration of ARDUAN®. Because ARDUAN® is never used alone and because the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of any anesthetic. In an animal study in MH-susceptible swine (n=7), the administration of ARDUAN® was not associated with the development of malignant hyperthermia.

Central Nervous System: ARDUAN® has no known effect on consciousness, the pain threshold, or cerebation. Therefore, administration must be accompanied by adequate anesthesia.

Drug Interactions: ARDUAN® can be administered following recovery from succinylcholine when the latter is used to facilitate endotracheal intubation.

The use of ARDUAN® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, is not recommended because it has not been studied.

There are no clinical data on concomitant use of ARDUAN® and other non-depolarizing neuromuscular blocking agents.

Inhalational Anesthetics: Use of volatile inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents on the order of enflurane > isoflurane > halothane. No definite interaction between ARDUAN® and halothane, as used clinically, has been demonstrated. Use of isoflurane in one study of 25 patients resulted in an increase in mean clinical duration by 12%. In another study of 25 patients first anesthetized with enflurane for 5 minutes or more, the mean clinical duration was increased by 50%. Therefore, a prolonged clinical duration following initial or maintenance doses and prolonged recovery from neuromuscular blocking effect of ARDUAN® should generally be anticipated with enflurane > isoflurane > halothane.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ARDUAN®. ARDUAN®-induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). In addition, experience with other drugs has suggested that acute (eg, diarrhea) or chronic (eg, adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, Sister Chromatid Exchange) conducted with ARDUAN® revealed no mutagenic potential.

Pregnancy Category C: A teratogenicity study has been conducted in rats using intravenously administered doses of ARDUAN® approximating the clinical dose in humans (50 µg/kg). No teratogenic effects were observed in this study. An embryotoxic effect (secondary to maternal toxicity) was observed at the highest dose administered (50 µg/kg) as demonstrated by an increase in earlier fetal resorptions. There are no adequate and well-controlled studies in pregnant women. ARDUAN® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Obstetrics (cesarean section): There are insufficient data on placental transfer of ARDUAN® and possible related effect(s) upon the neonate following cesarean section delivery. In addition, the duration of action of ARDUAN® exceeds the duration of operative obstetrics (cesarean section). Therefore, ARDUAN® is not recommended for use in patients undergoing C-section.

Pediatric Use: Infants (3 months to 1 year) under balanced anesthesia (2 studies in 52 infants), or halothane anesthesia (1 study in 29 infants), manifest similar dose response to ARDUAN® as do adults on a µg/kg ABW basis. Children (1 to 14 years) under balanced anesthesia (4 studies in 57 children), or halothane anesthesia (2 studies in 29 children), may be less sensitive than adults. These conclusions come from studies involving titrating patient response by the incremental method to approximately 1.2 times ED₅₀. There are no data on either onset time or clinical duration of larger doses in infants or children. There are no data on maintenance dosing in infants and children. Pharmacokinetic studies in infants and children have not been performed; therefore no pharmacokinetic modeling of incremental dosing can be attempted. The use of ARDUAN® in neonates and infants below 3 months of age has not been investigated. Antagonism has not been systematically studied in infants or children. However, usual clinical doses of neostigmine administered following significant levels of spontaneous recovery (recovery of T₁ to more than 50% of control) produced complete antagonism of residual neuromuscular block in less than 10 minutes in the majority of cases.

ADVERSE REACTIONS: The most frequent side effect of non-depolarizing blocking agents as a class is an extension of the drug's pharmacological action beyond the time period needed for surgery and anesthesia. Clinical signs may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. This may be due to the drug's effect or inadequate antagonism.

The following listings are based upon U.S. clinical studies involving nearly 600 patients utilizing a variety of premedications, varying lengths of surgical procedures, and various anesthetic agents.

Adverse experiences in greater than 1% of cases and judged by the investigator to have a possible causal relationship: clinically significant hypotension (2.5% of cases); clinically significant bradycardia (1.4% of cases).

Adverse experiences in less than 1% of cases and judged by the investigator to have a possible causal relationship:

Cardiovascular: hypertension, myocardial ischemia, cerebrovascular accident, thrombosis, atrial fibrillation, ventricular extrasystole.

Metabolic and Nutritional: increased creatinine, hypoglycemia, hyperkalemia.

Musculoskeletal: muscle atrophy, difficult intubation.

Nervous: hypesthesia, CNS depression.

Respiratory: dyspnea, respiratory depression, laryngismus, atelectasis.

Skin and Appendages: rash, urticaria.

Urogenital System: anuria.

HOW SUPPLIED: 10 mL vials containing 10 mg lyophilized pipecuronium bromide. Boxes of 6 (NDC 0052-0446-36) 10 mL vials containing 10 mg lyophilized pipecuronium bromide and 10 mL vials containing bacteriostatic water for injection, USP. Boxes of 6 (NDC 0052-0446-37)

Storage: 2°-30°C (36°-86°F). Protect from light.

After Reconstitution: When reconstituted with bacteriostatic water for injection, USP, CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

When reconstituted with sterile water for injection or other compatible IV solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REFERENCES

1. Data on file.
2. Folds FF, Nagashima H, Nguyen HD, Duncalf D, Goldiner PL. Neuromuscular and cardiovascular effects of pipecuronium. *Can J Anaesth.* 1990;37(5):549-555.
3. Larjani GE, Bartkowski RR, Azad SS, et al. Clinical pharmacology of pipecuronium bromide. *Anesth Analg.* 1989;68:734-739.
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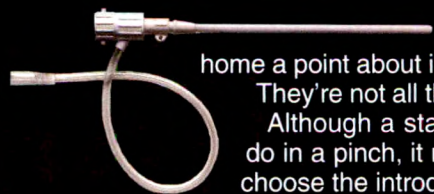
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MARCH 1991



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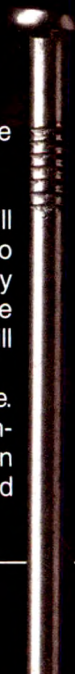
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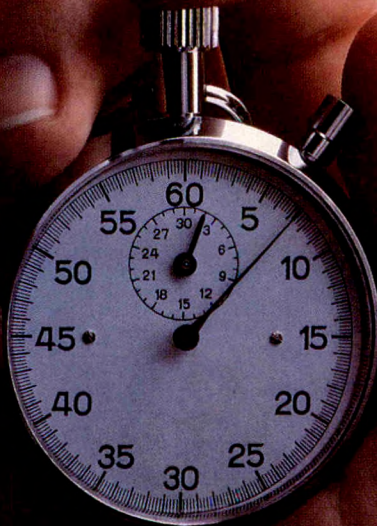
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Manuscripts and editorial correspondence should be addressed to: King Kryger, PhD, Managing Editor, *Anesthesia and Analgesia*, 3497 Sacramento Street, San Francisco, CA 94118 [telephone: (415) 292-7964; FAX: (415) 292-5157]. For information concerning preparation of manuscripts, see "A Guide for Authors" published quarterly in the Journal.

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FOR SHORTER SURGICAL PROCEDURES: THE ALFENTA ADVANTAGE

*As with all potent opioids, appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained. The duration and degree of respiratory depression and increased airway resistance usually increase with dose, but have also been observed at lower doses. Because of the possibility of delayed respiratory depression, monitoring of the patient must continue well after surgery.



Rapid-acting
Alfenta
(alfentanil HCl) Injection

For moment-to-moment
control of stress responses

RAPID ONSET

Rapidly blocks sympathetic
responses to induction
and intubation

SHORT DURATION

Results in quick recovery
of consciousness*

RAPID RECOVERY

Postoperative respiratory
depression is of short
duration*

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

CAUTION: Federal Law Prohibits Dispensing Without Prescription

DESCRIPTION: ALFENTA is a sterile, non-pyrogenic, preservative free aqueous solution containing alfentanil hydrochloride equivalent to 500 µg per ml of alfentanil base for intravenous injection. The solution, which contains sodium chloride for isotonicity, has a pH range of 4.0-5.0.

CONTRAINDICATIONS: ALFENTA (alfentanil hydrochloride) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: ALFENTA SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS AND GENERAL ANESTHETIC AGENTS AND IN THE MANAGEMENT OF RESPIRATORY EFFECTS OF POTENT OPIOIDS. AN OPIOID ANTAGONIST, RESUSCITATIVE AND INTUBATION EQUIPMENT AND OXYGEN SHOULD BE READILY AVAILABLE, BECAUSE OF THE POSSIBILITY OF DELAYED RESPIRATORY DEPRESSION. MONITORING OF THE PATIENT MUST CONTINUE WELL AFTER SURGERY. ALFENTA (alfentanil hydrochloride) administered in initial dosages up to 20 µg/kg may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence and severity of muscle rigidity is usually dose-related. Administration of ALFENTA at anesthetic induction dosages (above 130 µg/kg) will consistently produce muscular rigidity with an immediate onset. The onset of muscular rigidity occurs earlier than with other opioids. ALFENTA may produce muscular rigidity that involves all skeletal muscles, including those of the neck and extremities. The incidence may be reduced by: 1) routine methods of administration of neuromuscular blocking agents for balanced opioid anesthesia; 2) administration of up to 1/4 of the full paralyzing dose of a neuromuscular blocking agent just prior to administration of ALFENTA at dosages up to 130 µg/kg; following loss of consciousness, a full paralyzing dose of a neuromuscular blocking agent should be administered; or 3) simultaneous administration of ALFENTA and a full paralyzing dose of a neuromuscular blocking agent when ALFENTA is used in rapidly administered anesthetic dosages (above 130 µg/kg). The neuromuscular blocking agent used should be appropriate for the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered ALFENTA. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

PRECAUTIONS: DELAYED RESPIRATORY DEPRESSION, RESPIRATORY ARREST, BRADYCARDIA, ASYSTOLE, ARRHYTHMIAS AND HYPOTENSION HAVE ALSO BEEN REPORTED. THEREFORE, VITAL SIGNS MUST BE MONITORED CONTINUOUSLY.

General: The initial dose of ALFENTA (alfentanil hydrochloride) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. In one clinical trial, the dose of ALFENTA required to produce anesthesia, as determined by appearance of delta waves in EEG, was 40% lower in geriatric patients than that needed in healthy young patients. In patients with compromised liver function and in geriatric patients, the plasma clearance of ALFENTA may be reduced and postoperative recovery may be prolonged. Induction doses of ALFENTA should be administered slowly (over three minutes). Administration may produce loss of vascular tone and hypotension. Consideration should be given to fluid replacement prior to induction. Diazepam administered immediately prior to or in conjunction with high doses of ALFENTA may produce vasodilation, hypotension and result in delayed recovery. Bradycardia produced by ALFENTA may be treated with atropine. Severe bradycardia and asystole have been successfully treated with atropine and conventional resuscitative methods. The hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required should be considered in the selection of a neuromuscular blocking agent. Following an anesthetic induction dose of ALFENTA, requirements for volatile inhalation anesthetics or ALFENTA infusion are reduced by 30 to 50% for the first hour of maintenance. Administration of ALFENTA infusion should be discontinued at least 10-15 minutes prior to the end of surgery. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by ALFENTA may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Intraoperative hyperventilation may further alter postoperative response to CO₂. Appropriate postoperative monitoring should be employed, particularly after infusions and large doses of ALFENTA, to ensure that adequate spontaneous breathing is established and maintained in the absence of stimulation prior to discharging the patient from the recovery area.

Head Injuries: ALFENTA may obscure the clinical course of patients with head injuries.

Impaired Respiration: ALFENTA should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration.

Impaired Hepatic or Renal Function: In patients with liver or kidney dysfunction, ALFENTA should be administered with caution due to the importance of these organs in the metabolism and excretion of ALFENTA.

Drug Interactions: Both the magnitude and duration of central nervous system and cardiovascular effects may be enhanced when ALFENTA is administered in combination with other CNS depressants such as barbiturates, tranquilizers, opioids, or inhalation general anesthetics. Postoperative respiratory depression may be enhanced or prolonged by these agents. In such cases of combined treatment, the dose of one or both agents should be reduced. Limited clinical evidence indicates that requirements for volatile inhalation anesthetics are reduced by 30 to 50% for the first sixty (60) minutes following ALFENTA induction. The concomitant use of erythromycin with ALFENTA can significantly inhibit ALFENTA clearance and may increase the risk of prolonged or delayed respiratory depression. Perioperative administration of drugs affecting hepatic blood flow or enzyme function may reduce plasma clearance and prolong recovery.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No long-term animal studies of ALFENTA have been performed to evaluate carcinogenic potential. The micronucleus test in female rats and the dominant lethal test in female and male mice revealed that single intravenous doses of ALFENTA as high as 20 mg/kg (approximately 40 times the upper human dose) produced no structural chromosome mutations or induction of dominant lethal mutations. The Ames Salmonella typhimurium metabolic activating test also revealed no mutagenic activity.

Pregnancy Category C: ALFENTA has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects could have been due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects has been observed after administration of ALFENTA in rats or rabbits. There are no adequate and well-controlled studies in pregnant women. ALFENTA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: There are insufficient data to support the use of ALFENTA in labor and delivery. Placental transfer of the drug has been reported; therefore, use in labor and delivery is not recommended.

Nursing Mothers: In one study of nine women undergoing post-partum tubal ligation, significant levels of ALFENTA were detected in colostrum four hours after administration of 60 µg/kg of ALFENTA, with no detectable levels present after 28 hours. Caution should be exercised when ALFENTA is administered to a nursing woman.

Pediatric Use: Adequate data to support the use of ALFENTA in children under 12 years of age are not presently available.

ADVERSE REACTIONS: The most common adverse reactions, respiratory depression and skeletal muscle rigidity, are extensions of known pharmacological effects of opioids. See CLINICAL PHARMACOLOGY, WARNINGS AND PRECAUTIONS on the management of respiratory depression and skeletal muscle rigidity. Delayed respiratory depression, respiratory arrest, bradycardia, asystole, arrhythmias and hypotension have also been reported. The reported incidences of adverse reactions listed in the following table are derived from controlled and open clinical trials involving 1183 patients, of whom 785 received ALFENTA. The controlled trials involved treatment comparisons with fentanyl, thiopental sodium, enflurane, saline placebo and halothane. Incidences are based on disturbing and non-disturbing adverse reactions reported. The comparative incidence of certain side effects is influenced by the type of use, e.g., chest wall rigidity has a higher reported incidence in clinical trials of alfentanil induction, and by the type of surgery, e.g., nausea and vomiting have a higher incidence in patients undergoing gynecologic surgery.

Percent	ALFENTA (N=785)	Fentanyl (N=243)	Thiopental Sodium (N=66)	Enflurane (N=55)	Halothane (N=18)	Saline Placebo* (N=18)
Gastrointestinal						
Nausea	28	44	14	5	0	22
Vomiting	18	31	11	9	13	17
Cardiovascular						
Bradycardia	14	7	8	0	0	0
Tachycardia	12	12	39	36	31	11
Hypertension	10	8	7	7	0	0
Hypotension	18	13	30	20	6	0
Arrhythmia	2	2	5	4	6	0
Musculoskeletal						
Chest Wall	17	12	0	0	0	0
Rigidity						
Skeletal Muscle	6	2	6	2	0	0
Movements						
Respiratory						
Apnea	7	0	0	0	0	0
Postoperative	2	2	0	0	0	0
Respiratory						
Depression						
CNS						
Dizziness	3	5	0	0	0	0
Sleepiness/	2	8	2	0	0	6
Postoperative						
Sedation						
Blurred Vision	2	2	0	0	0	0

*From two clinical trials, one involving supplemented balanced barbiturate/nitrous oxide anesthesia and one in healthy volunteers who did not undergo surgery.

In addition, other adverse reactions less frequently reported (1% or less) were: Laryngospasm, bronchospasm, postoperative confusion, headache, shivering, postoperative euphoria, hypercarbia, pain on injection, urticaria, and itching. Some degree of skeletal muscle rigidity should be expected with induction doses of ALFENTA.

DRUG ABUSE AND DEPENDENCE: ALFENTA (alfentanil hydrochloride) is a Schedule II controlled drug substance that can produce drug dependence of the morphine type and therefore has the potential for being abused.

OVERDOSAGE: Overdosage would be manifested by extension of the pharmacological actions of ALFENTA (alfentanil hydrochloride) (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. No experience of overdosage with ALFENTA was reported during clinical trials. The intravenous LD₅₀ of ALFENTA is 43.0-50.9 mg/kg in rats, 72.2-73.6 mg/kg in mice, 71.8-81.9 mg/kg in guinea pigs and 59.5-87.5 mg/kg in dogs. Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with ALFENTA may be longer than the duration of action of the opioid antagonist. Administration of an opioid antagonist should not preclude immediate establishment of a patent airway, administration of oxygen, and assisted or controlled ventilation as indicated for hyperventilation or apnea. If respiratory depression is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled ventilation. Intravenous fluids and vasoactive agents may be required to manage hemodynamic instability.

DOSE AND ADMINISTRATION: The dosage of ALFENTA (alfentanil hydrochloride) should be individualized in each patient according to body weight, physical status, underlying pathological condition, use of other drugs, and type and duration of surgical procedure and anesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of ALFENTA should be determined on the basis of lean body weight. The dose of ALFENTA should be reduced in elderly or debilitated patients (see PRECAUTIONS). Vital signs should be monitored routinely. Protect from light. Store at room temperature 15°-30° C (59°-86° F).

Manufactured by Taylor Pharmacal Co. for



**JANSSEN
PHARMACEUTICA**

Piscataway, N.J. 08854

March 1987, April 1988
U.S. Patent No. 4,167,574
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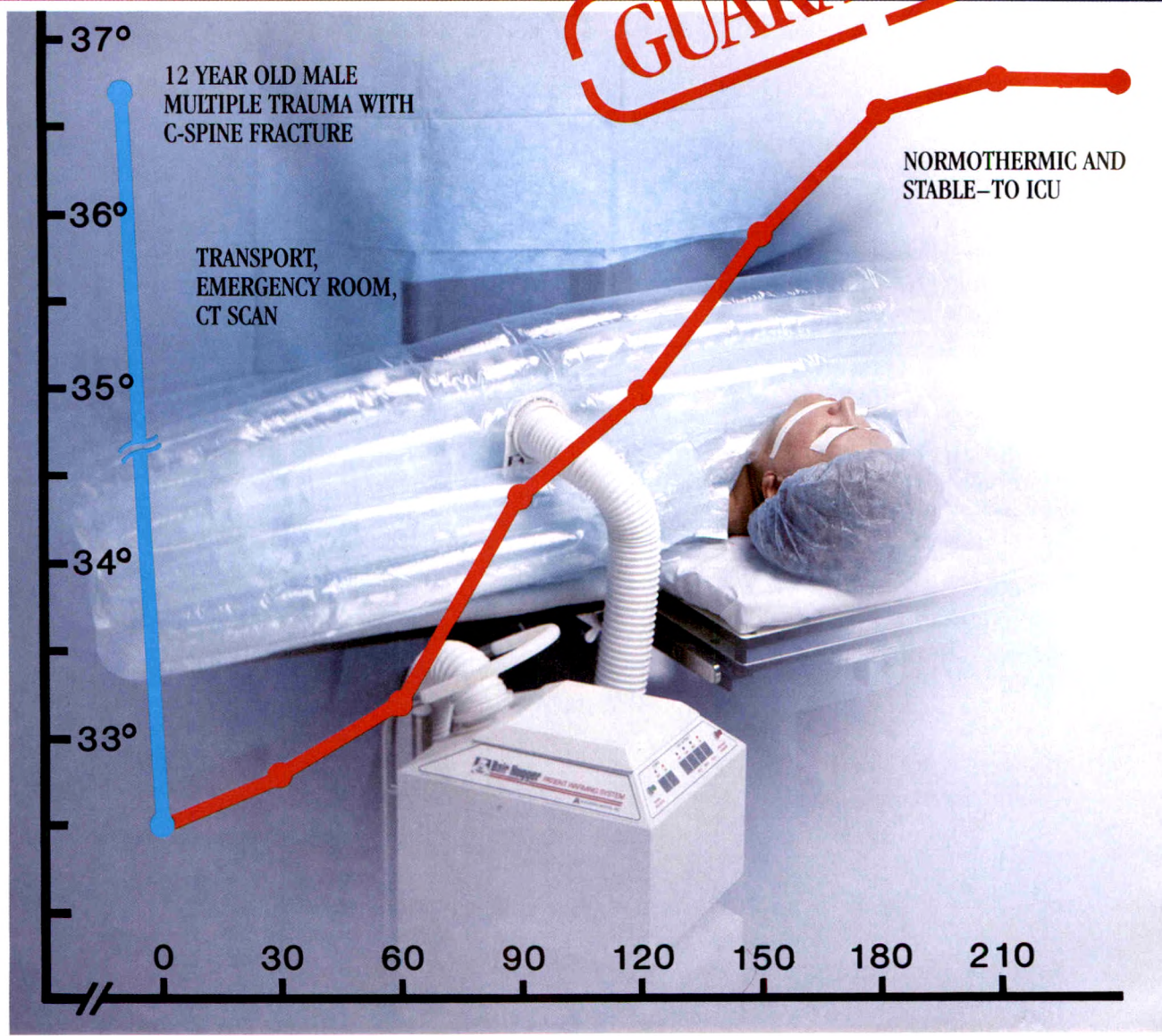
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A synergy of effects and advantages

Co-induction—when two or more agents rather than one are used for induction—may offer clinical benefits if there is anesthetic synergy. Specifically, subanesthetic doses of each agent may produce a prompt, short-acting effect with more stable

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A classic example of synergy is mutual enhancement of receptor-site affinity: *e.g.*, a benzodiazepine such as VERSED may alter barbiturate receptors in a way that enhances barbiturate effects. Likewise, a barbiturate may potentiate

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CO-INDUCTION OF ANESTHESIA

Lower doses of both agents

Several studies have shown that a small initial dose of VERSED will allow lower induction doses of thiopental, methohexital, fentanyl, alfentanil or ketamine.^{1,4-9}

In one study of 90 unpremedicated ASA Class I & II patients, co-induction with VERSED followed by thiopental required just 1/4 of each drug's usual ED₅₀.⁵

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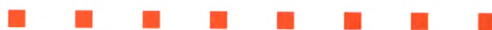
Therefore, a VERSED co-induction may reduce the possibility of recall (*e.g.*, during intubation) in the event of lightening of anesthesia with short-acting hypnotics such as thiopental or propofol.

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As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (*e.g.*, drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

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Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of under-ventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combative-ness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Use in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

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2. Inform your physician if you are pregnant or are planning to become pregnant.

3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and Innoval (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine. No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section. Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm. Gastrointestinal: Acid taste, excessive salivation, retching. CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphonia, paraesthesia. Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSEAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam.

BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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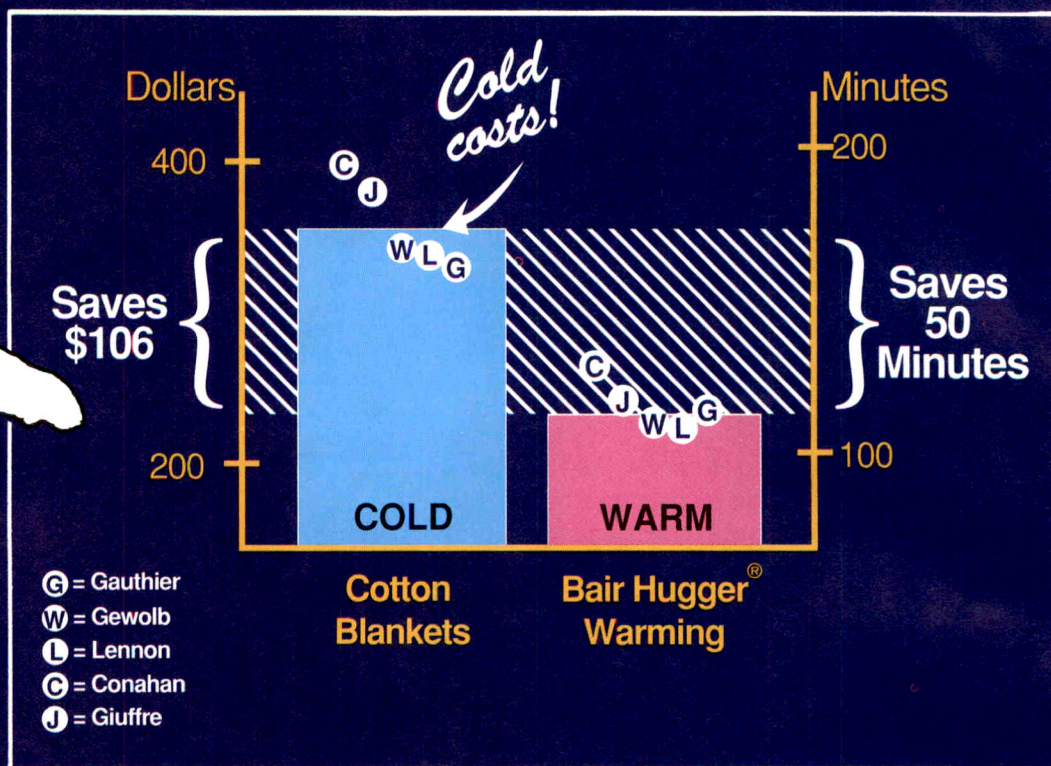
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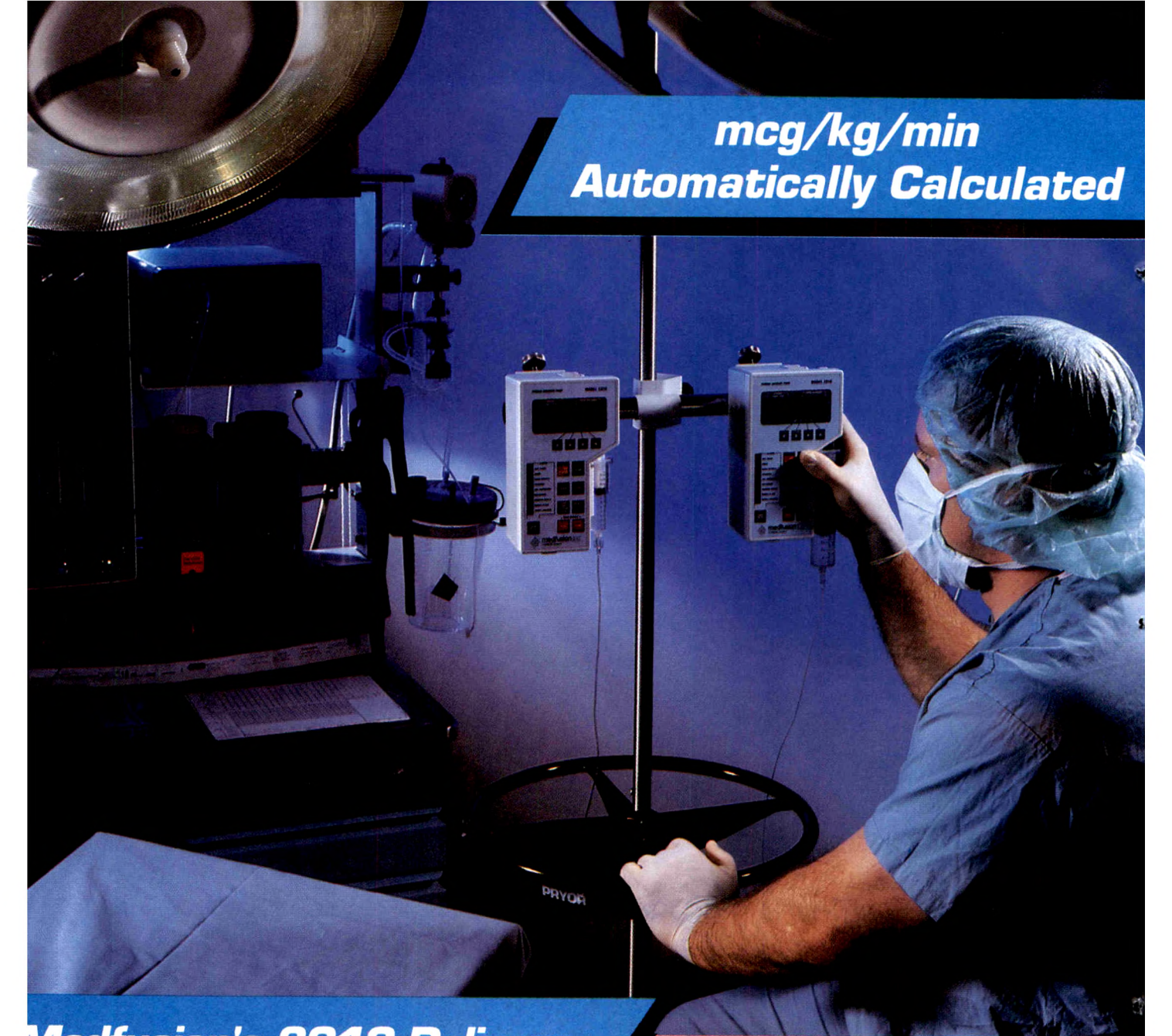


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Needles: A Sticky Situation for U.S. Healthcare.

Healthcare workers in America are facing an epidemic problem – needle sticks. Each year thousands of healthcare workers are accidentally stuck in hospitals, nursing homes, clinics and in general practice. These needle sticks can lead to very serious infections, with at least 20 percent pathogens having been identified as transmitted in this way.

In fact, the New England Journal of Medicine reported in its August 4th issue that as many as 12,000 healthcare providers contract hepatitis each year. A large segment of the universe infected by accidental needle sticks. The seriousness can be seen in this statistic: 1

200 to 300 deaths a year to healthcare providers. And the number is growing every year. Add to this fact that the danger is now compounded by the AIDS virus and you can see just how critical the problem of needle sticks truly is.

According to the Center for Disease Control in Atlanta, Georgia, a healthcare professional has a one in 200 chance of contracting AIDS from a contaminated needle and industry sources report that over 800,000 needle sticks occur each year in hospitals alone. With these kinds of statistics it is no wonder that the healthcare professions are seeking solutions to this massive problem. To look at the problem from another point of view, consider the cost of this epidemic. It is estimated between \$400 million and \$1.0 billion is spent per year in direct costs arising from needle sticks and

this range does not include treatment or loss of work. In other words, aside from the human suffering associated with the infamous needle stick, the pocket book is infected, too.

One of the solutions to this huge problem facing the healthcare field today is the reduction of the total number of needles used in practice. One example of how the demand for needles can be reduced is the utilization of I.V. sets that provide luer connections which do not require needles.

With more than an estimated 1-million needle sticks per year, the situation is getting worse, not better. Until a solution is found, the American healthcare system will be under siege from the needle. What was once designed to deliver healing is now dealing misery – the needle: a sticky situation the U.S. healthcare profession must face.

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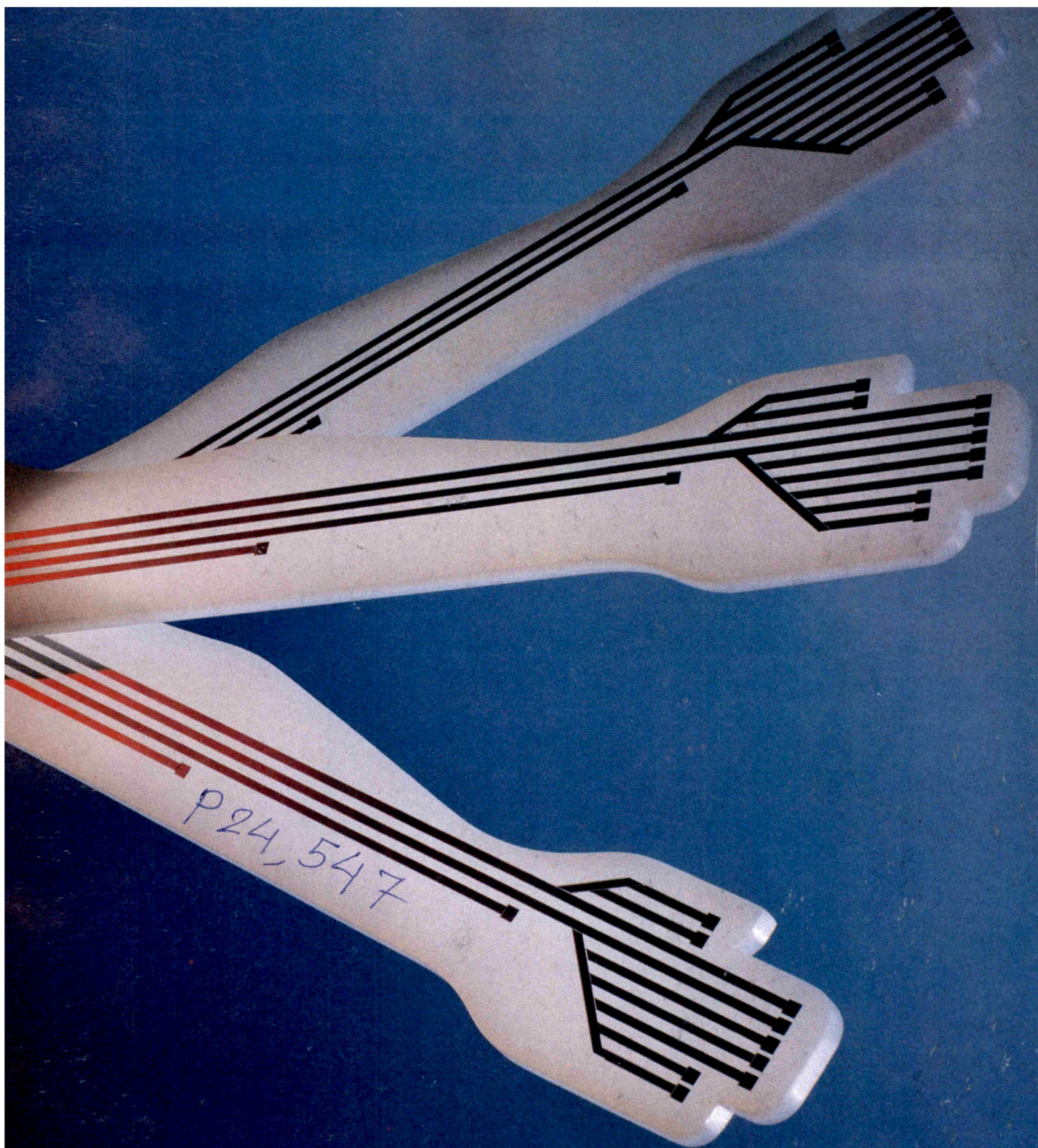
product line make great sense for the OR, but in ICU and CCU as well.

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HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance. ¹	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance. ¹ ($P < .05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur. ¹⁻⁴	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma) ⁵
RECOVERY To 25% of control To 95% of control	25–45 min ³ 45–65 min ³	35–45 min ⁵ 60–70 min ⁵
DOSING FLEXIBILITY	The initial recommended dose is 0.08–0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects. ^{1,3,4}	Initial recommended dose is 0.4–0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P < .05$) and 0.6 mg/kg.* ^{2,5,6}
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature. [†] Can be reconstituted with various IV solutions including Lactated Ringers. [‡]	2-year shelf life under constant refrigeration. [†] Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated. ⁵

*Dose of atracurium above 0.5 mg/kg is not recommended.

‡Storage after reconstitution varies with solution. See package insert.

†As originally supplied by the respective manufacturers.

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.



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Norcuron[®]

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron[®] is contraindicated in patients known to have a hypersensitivity to it. **WARNINGS:** NORCURON[®] SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron[®] may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron[®] is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron[®] should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, anemias, states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron[®] metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in ICU: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypokalemic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron[®].

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron[®] is capable of triggering malignant hyperthermia. **C.N.S.:** Norcuron[®] has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron[®] (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron[®], the administration of Norcuron[®] should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron[®] may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron[®] before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron[®], therefore these drugs and Norcuron[®] may exert an additive effect when used together. There are insufficient data to support concomitant use of Norcuron[®] and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron[®] will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron[®] may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin and sodium colistimethate.

Other: Experience on morning injection of quinine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron[®]. Norcuron[®] induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Cardiac effects, Hematogenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate cardiotoxic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron[®]. Norcuron[®] should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron[®] on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for use in neonates.

ADVERSE REACTIONS: Norcuron[®] was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron[®] as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron[®] is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances. **OVERDOSAGE:** The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron[®] produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with Norcuron[®] as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol[®] (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron[®]. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSEAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron[®] (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron[®] by volatile

anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron[®] and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron[®] is 0.06 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalational anesthetics, the neuromuscular blocking effect of Norcuron[®] is enhanced. If Norcuron[®] is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron[®] dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron[®]. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron[®] to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron[®] are recommended; after the initial Norcuron[®] injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron[®] lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use in Cardiovascular Inhibition: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron[®] should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron[®] should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron[®] infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron[®] can be prepared by mixing Norcuron[®] with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron[®] can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron[®] in 100 mL solution
†20 mg of Norcuron[®] in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON[®] INFUSION RATE — mL/MIN

Amount of Drug µg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron[®] on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron[®] is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEONATES. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3/89

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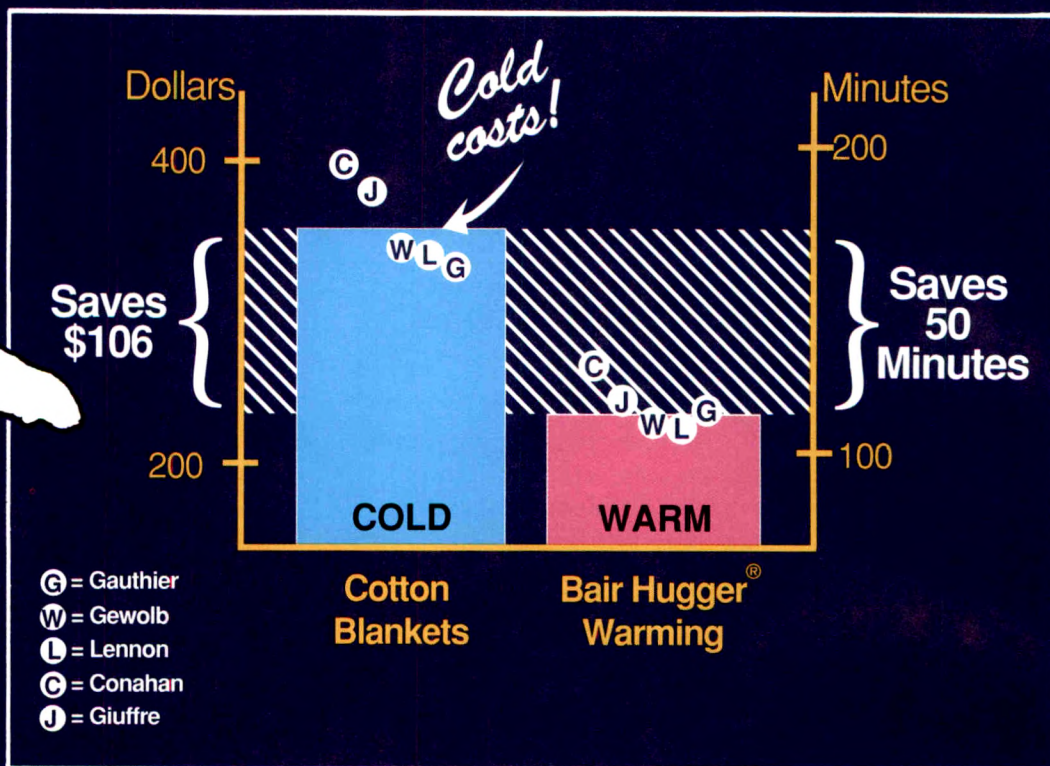
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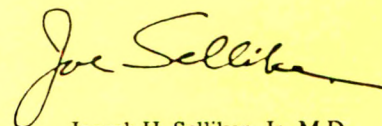
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Optimal induction produces 1) unconsciousness and 2) a rapid progression to a state of anesthesia, with maintenance of stable cardiovascular functioning.¹

However, even though high doses of hypnotics—such as thiopental or propofol—can achieve both endpoints, they can also cause significant hemodynamic changes. Therefore, it may be advantageous to manage hypnosis and anesthesia sequentially by employing a combination of function-specific agents.

Indeed, VERSED given in combination with a second agent can achieve hypnosis through the synergistic interaction of subanesthetic doses,²⁻⁸ the goal being to maximize desired effects and reduce the undesired.

THE SYNERGY OF CO-INDUCTION

The advantage of co-induction

It is well established that induction agents potentiate each other when given in combination. One quarter of the hypnotic ED₅₀ of VERSED can reduce the hypnotic ED₅₀ of thiopental by as much as 75%.³

However, this degree of reduction occurs when thiopental is given one minute after VERSED, thereby achieving synchronous peak effects. The magnitude of interaction diminishes as the interval between the administration of the co-induction agents lengthens.

Dosing considerations with VERSED® (midazolam HCl/Roche)®

When VERSED is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia, whichever is longer. The decision must be individualized.

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References: 1. Willebrand RL. Management of general anesthesia. In: Miller RD, ed. *Anesthesia*. 3rd ed. New York: Churchill Livingstone; 1990:1335-1346. 2. Vinik HR, Bradley EL Jr, Klein I. Midazolam for induction of thiopental anesthesia in patients. *Anesthesiology*. 1990;73(3A):A1216. 3. Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg*. 1989;67:342-345. 4. Tverskoy M, et al. Midazolam acts synergistically with methohexital for induction of anesthesia. *Br J Anaesth*. 1989;63:100-112. 5. Short TG, Gaffney DG, Plummer JL. Hypnotic and anesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth*. 1991;66:13-19. 6. Klein I, et al. Allantoin potentiates midazolam-induced unconsciousness in subanesthetic doses. *Anesth Analg*. 1990;71:65-69. 7. Vinik HR, Bradley EL Jr, Klein I. Midazolam-allantoin synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69:213-217. 8. Ben-Shalom I, et al. Midazolam acts synergistically with fentanyl for induction of anesthesia. *Br J Anaesth*. 1990;64:45-47.

VERSED® (midazolam HCl/Roche) @ INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 1 mg/mL or 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of underventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combative-ness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chloridiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicine you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines. 2. Inform your physician if you are pregnant or are planning to become pregnant.

VERSED® (midazolam HCl/Roche)

3. Inform your physician if you are nursing.

Drug interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine. No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/laboratory test interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.

Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: Respiratory: Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching. CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, ataxic movements, ataxia, dizziness, dysphoria, slurred speech, dysphoria, paresthesia. Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus. Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam. BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

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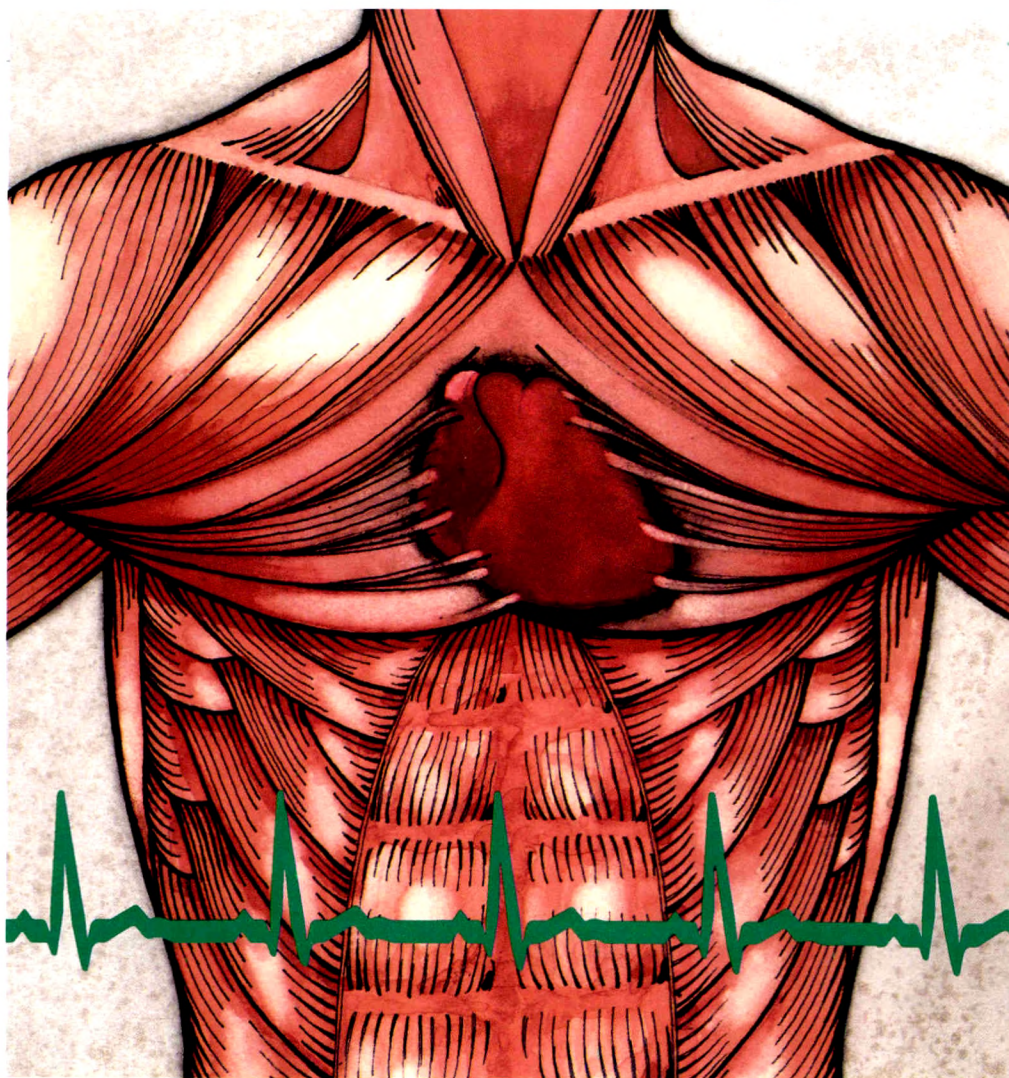
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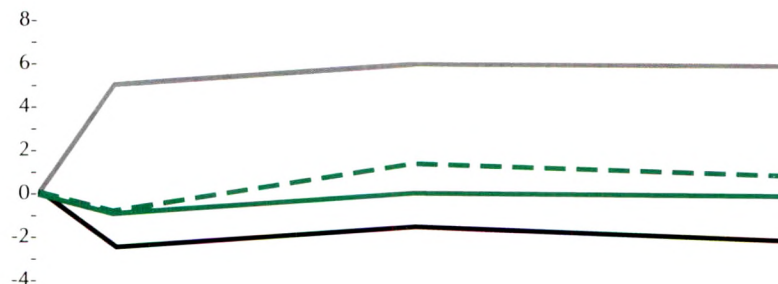
A Long-Acting Neuromuscular Blocker

NUROMAX[®] INJECTION (doxacurium chloride)

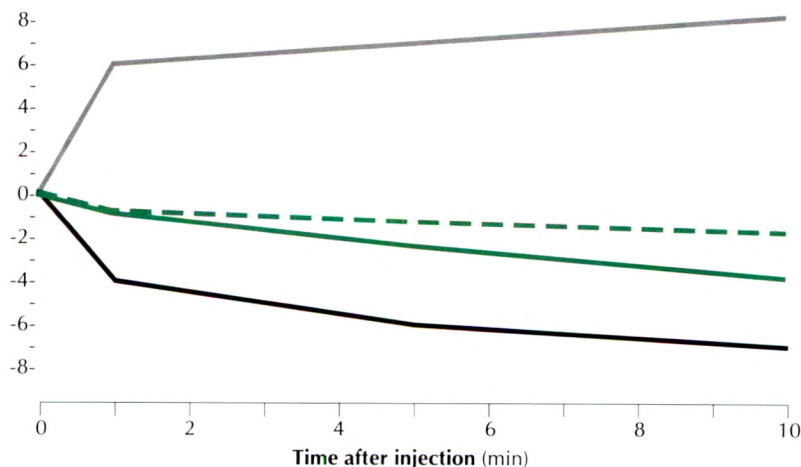
Excellent CV Stability

Cardiovascular stability comparable with vecuronium

Change in MAP
(mm/Hg)



Change in HR
(beats/min)



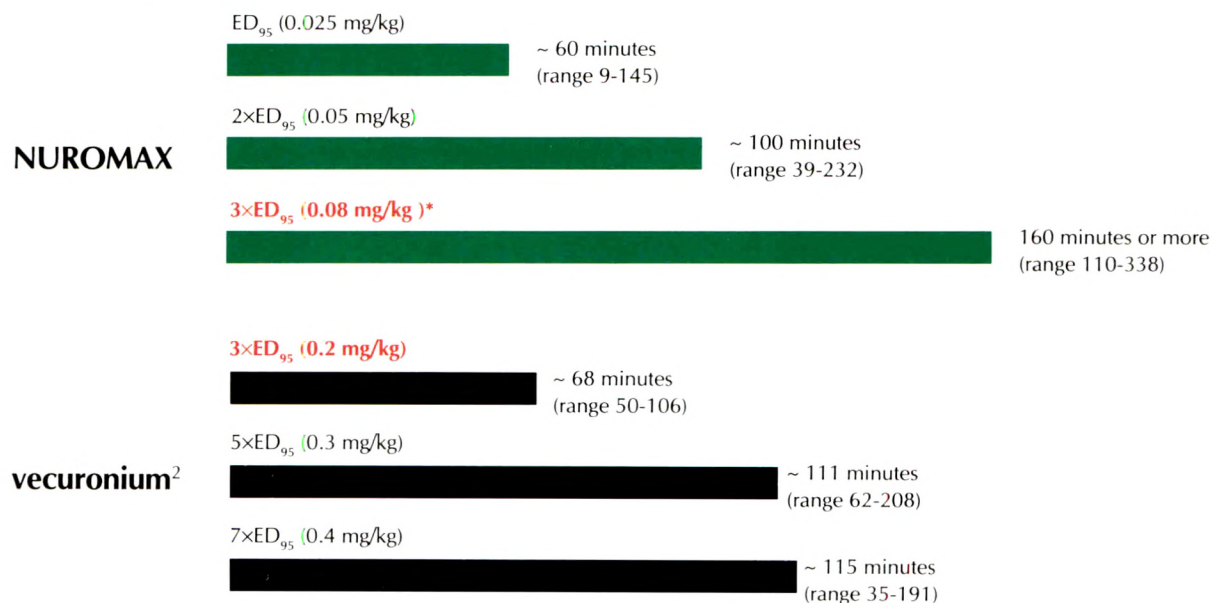
Emmott et al¹ compared the hemodynamic effects of Nuromax 0.037 and 0.075 mg/kg with the effects of pancuronium 0.09 mg/kg and vecuronium 0.075 mg/kg in 36 CABG patients (9 patients, each group). Mean changes from baseline values of mean systemic arterial pressure (MAP) and heart rate (HR) at 1, 5 and 10 min after administration. All routine cardiac and vasoactive medications were continued up to the morning of surgery.

— doxacurium 0.037 mg/kg — pancuronium 0.09 mg/kg
— doxacurium 0.075 mg/kg — vecuronium 0.075 mg/kg



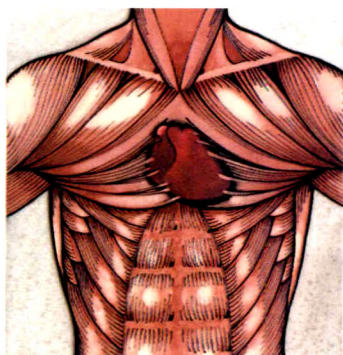
Longer acting than “high-dose” vecuronium

Clinically effective block (time to 25% recovery)



*This dose should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated.

- Cardiovascular stability comparable with normal saline³
- Noncumulative
- Ready-to-use solution
- Vials stored at room temperature, no refrigeration required
- Supplied as a 5 mL vial, 1 mg/mL



NUROMAX[®] INJECTION
(doxacurium chloride) 1 mg/mL
Excellent for Long CV Procedures



Please see full prescribing information on following pages.

NUROMAX[®] INJECTION (DOXACURIUM CHLORIDE)

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: Nuromax (doxacurium chloride) is a long-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Doxacurium chloride is *trans, trans*-2,2'-(succinylbis[oxymethylene])bis[1,2,3,4-tetrahydro-6,7,8-trimethoxy-2-methyl-1-(3,4,5-trimethoxybenzyl)isoquinolinium] dichloride. The molecular formula is $C_{26}H_{38}Cl_2N_2O_{16}$ and the molecular weight is 1106.14. The compound does not partition into the 1-octanol phase of a distilled water/1-octanol system, i.e., the n-octanol/water partition coefficient is 0.

Doxacurium chloride is a mixture of three *trans, trans* stereoisomers, a *dl* pair [(1*R*, 1'*R*, 2*S*, 2'*S*) and (1*S*, 1'*S*, 2*R*, 2'*R*)] and a meso form (1*R*, 1'*S*, 2*S*, 2'*R*).

Nuromax Injection is a sterile, non-pyrogenic aqueous solution (pH 3.9 to 5.0) containing doxacurium chloride equivalent to 1 mg/mL doxacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. Nuromax Injection contains 0.9% w/v benzyl alcohol.

CLINICAL PHARMACOLOGY: Nuromax binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: Nuromax is approximately 2.5 to 3 times more potent than pancuronium and 10 to 12 times more potent than metocurine. Nuromax in doses of 1.5 to 2 x ED₉₅ has a clinical duration of action (range and variability) similar to that of equipotent doses of pancuronium and metocurine (historic data and limited comparison). The average ED₉₅ (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of Nuromax is 0.025 mg/kg (range: 0.020 to 0.033) in adults receiving balanced anesthesia.

The onset and clinically effective duration (time from injection to 25% recovery) of Nuromax administered alone or after succinylcholine during stable balanced anesthesia are shown in Table 1.

TABLE 1
Pharmacodynamic Dose Response* Balanced Anesthesia

	Initial Nuromax Dose (mg/kg)		
	0.025 [†] (n=34)	0.05 (n=27)	0.08 (n=9)
Time to Maximum Block (min)	9.3 (5.4-16)	5.2 (2.5-13)	3.5 (2.4-5)
Clinical Duration (min) (Time to 25% Recovery)	55 (9-145)	100 (39-232)	160 (110-338)

* Values shown are means (range).

[†] Nuromax administered after 10% to 100% recovery from an intubating dose of succinylcholine.

Initial doses of 0.05 mg/kg (2 x ED₉₅) and 0.08 mg/kg (3 x ED₉₅) Nuromax administered during the induction of thiopental-narcotic anesthesia produced good-to-excellent conditions for tracheal intubation in 5 minutes (13 of 15 cases studied) and 4 minutes (8 of 9 cases studied) (which are before maximum block), respectively.

As with other long-acting agents, the clinical duration of neuromuscular block associated with Nuromax shows considerable interpatient variability. An analysis of 390 cases in U.S. clinical trials utilizing a variety of premedications, varying lengths of surgery, and various anesthetic agents, indicates that approximately two-thirds of the patients had clinical durations within 30 minutes of the duration predicted by dose (based on mg/kg actual body weight). Patients ≥ 60 years old are approximately twice as likely to experience prolonged clinical duration (30 minutes longer than predicted) than patients < 60 years old; thus, care should be used in older patients when prolonged recovery is undesirable (see **Geriatric Use** subsection of PRECAUTIONS and **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). In addition, obese patients (patients weighing ≥ 30% more than ideal body weight for height) were almost twice as likely to experience prolonged clinical duration than non-obese patients; therefore, dosing should be based on ideal body weight (IBW) for obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

The mean time for spontaneous T₁ recovery from 25% to 50% of control following initial doses of Nuromax is approximately 26 minutes (range: 7 to 104, n=253) during balanced anesthesia. The mean time for spontaneous T₁ recovery from 25% to 75% is 54 minutes (range: 14 to 184, n=184).

Most patients receiving Nuromax in clinical trials required pharmacologic reversal prior to full spontaneous recovery from neuromuscular block (see **Antagonism of Neuromuscular Block** subsection of OVERDOSAGE); therefore, relatively few data are available on the time from injection to 95% spontaneous recovery of the twitch response. As with other long-acting neuromuscular blocking agents, Nuromax may be associated with prolonged times to full spontaneous recovery. Following an initial dose of 0.025 mg/kg Nuromax, some patients may require as long as 4 hours to exhibit full spontaneous recovery.

Cumulative neuromuscular blocking effects are not associated with repeated administration of maintenance doses of Nuromax at 25% T₁ recovery. As with initial doses, however, the duration of action following maintenance doses of Nuromax may vary considerably among patients.

The Nuromax ED₉₅ for children 2 to 12 years of age receiving halothane anesthesia is approximately 0.03 mg/kg. Children require higher Nuromax doses on a mg/kg basis than adults to achieve comparable levels of block. The onset time and duration of block are shorter in children than adults. During halothane anesthesia, doses of 0.03 mg/kg and 0.05 mg/kg Nuromax produce maximum block in approximately 7 and 4 minutes, respectively. The duration of clinically effective block is approximately 30 minutes after an initial dose of 0.03 mg/kg and approximately 45 minutes after 0.05 mg/kg. Nuromax has not been studied in children below the age of 2 years.

The neuromuscular block produced by Nuromax may be antagonized by anticholinesterase agents. As with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at reversal, the longer the time and the greater the dose of anticholinesterase required for recovery of neuromuscular function.

Hemodynamics: Administration of Nuromax doses up to and including 0.08 mg/kg (~3 x ED₉₅) over 5 to 15 seconds to healthy adult patients during stable state balanced anesthesia and to patients with serious cardiovascular disease undergoing coronary artery bypass grafting, cardiac valvular repair, or vascular repair produced no dose-related effects on mean arterial blood pressure (MAP) or heart rate (HR).

No dose-related changes in MAP and HR were observed following administration of up to 0.05 mg/kg Nuromax over 5 to 15 seconds in 2- to 12-year-old children receiving halothane anesthesia.

Doses of 0.03 to 0.08 mg/kg (1.2 to 3 x ED₉₅) were not associated with dose-dependent changes in mean plasma histamine concentration. Clinical experience with more than 1,000 patients indicates that adverse experiences typically associated with histamine release (e.g., bronchospasm, hypotension, tachycardia, cutaneous flushing, urticaria, etc.) are very rare following the administration of Nuromax (see ADVERSE REACTIONS).

Pharmacokinetics: Pharmacokinetic and pharmacodynamic results from a study of 24 healthy young adult patients and 8 healthy elderly patients are summarized in Table 2. The pharmacokinetics are linear over the dosage range tested (i.e., plasma concentrations are approximately proportional to dose). The pharmacokinetics of Nuromax are similar in healthy young adult and elderly patients. Some healthy elderly patients tend to be more sensitive to the neuromuscular blocking effects of Nuromax than healthy young adult patients receiving the same dose. The time to maximum block is longer in elderly patients than in young adult patients (11.2 minutes versus 7.7 minutes at 0.025 mg/kg Nuromax). In addition, the clinically effective durations of block are more variable and tend to be longer in healthy elderly patients than in healthy young adult patients receiving the same dose.

TABLE 2
Pharmacokinetic and Pharmacodynamic Parameters* of Nuromax in Young Adult and Elderly Patients (Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients (22 to 49 yrs)			Healthy Elderly Patients (67 to 72 yrs)
	0.025 mg/kg (n=8)	0.05 mg/kg (n=8)	0.08 mg/kg (n=8)	0.025 mg/kg (n=8)
t _{1/2} elimination (min)	86 (25-171)	123 (61-163)	98 (47-163)	96 (50-114)
Volume of Distribution at Steady State (L/kg)	0.15 (0.10-0.21)	0.24 (0.13-0.30)	0.22 (0.16-0.33)	0.22 (0.14-0.40)
Plasma Clearance (mL/min/kg)	2.22 (1.02-3.95)	2.62 (1.21-5.70)	2.53 (1.88-3.38)	2.47 (1.58-3.60)
Maximum Block (%)	97 (88-100)	100 (100-100)	100 (100-100)	96 (90-100)
Clinically Effective Duration of Block [‡] (min)	68 (35-90)	91 (47-132)	177 (74-268)	97 (36-179)

1 Values shown are means (range).

2 Time from injection to 25% recovery of the control twitch height.

Table 3 summarizes the pharmacokinetic and pharmacodynamic results from a study of 9 healthy young adult patients, 8 patients with end-stage kidney disease undergoing kidney transplantation, and 7 patients with end-stage liver disease undergoing liver transplantation. The results suggest that a longer t_{1/2} can be expected in patients with end-stage kidney disease; in addition, these patients may be more sensitive to the neuromuscular blocking effects of Nuromax. The time to maximum block was slightly longer and the clinically effective duration of block was prolonged in patients with end-stage kidney disease.

TABLE 3
Pharmacokinetic and Pharmacodynamic Parameters* of Nuromax in Healthy Patients and in Patients Undergoing Kidney or Liver Transplantation (Isoflurane Anesthesia)

Parameter	Healthy Young Adult Patients	Kidney Transplant Patients	Liver Transplant Patients
	0.015 mg/kg (n=9)	0.015 mg/kg (n=8)	0.015 mg/kg (n=7)
t _{1/2} elimination (min)	99 (48-193)	221 (84-592)	115 (69-148)
Volume of Distribution at Steady State (L/kg)	0.22 (0.11-0.43)	0.27 (0.17-0.55)	0.29 (0.17-0.35)
Plasma Clearance (mL/min/kg)	2.66 (1.35-6.66)	1.23 (0.48-2.40)	2.30 (1.96-3.05)
Maximum Block (%)	86 (59-100)	98 (95-100)	70 (0-100)
Clinically Effective Duration of Block (min)	36 (19-80)	80 (29-133)	52 (20-91)

1 Values shown are means (range).

No data are available from patients with liver disease not requiring transplantation. There are no significant alterations in the pharmacokinetics of Nuromax in liver transplant patients. Sensitivity to the neuromuscular blocking effects of Nuromax was highly variable in patients undergoing liver transplantation. Three of 7 patients developed ≤ 50% block, indicating that a reduced sensitivity to Nuromax may occur in such patients. In those patients who developed > 50% neuromuscular block, the time to maximum block and the clinically effective duration tended to be longer than in healthy young adult patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Consecutively administered maintenance doses of 0.005 mg/kg Nuromax, each given at 25% T₁ recovery following the preceding dose, do not result in a progressive increase in the plasma concentration of doxacurium or a progressive increase in the depth or duration of block produced by each dose.

Nuromax is not metabolized *in vitro* in fresh human plasma. Plasma protein binding of Nuromax is approximately 30% in human plasma.

In vivo data from humans suggest that Nuromax is not metabolized and that the major elimination pathway is excretion of unchanged drug in urine and bile. In studies of healthy adult patients, 24% to 38% of an administered dose was recovered as parent drug in urine over 6 to 12 hours after dosing. High bile concentrations of Nuromax (relative to plasma) have been found 35 to 90 minutes after administration. The overall extent of biliary excretion is unknown. The data derived from analysis of human urine and bile are consistent with data from *in vivo* studies in the rat, cat, and dog, which indicate that all of an administered dose of Nuromax is recovered as parent drug in the urine and bile of these species.

Individualization of Dosages: In elderly patients or patients who have impaired renal function, the potential for a prolongation of block may be reduced by decreasing the initial Nuromax dose and by titrating the dose to achieve the desired depth of block. In obese patients (patients weighing ≥ 30% more than ideal body weight for height), the Nuromax dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg = [106 + (6 x inches in height above 5 feet)]/2.2

Women: IBW in kg = [100 + (5 x inches in height above 5 feet)]/2.2

Dosage requirements for patients with severe liver disease are variable; some patients may require a higher than normal initial Nuromax dose to achieve clinically effective block. Once adequate block is established, the clinical duration of block may be prolonged in such patients relative to patients with normal liver function.

As with pancuronium, metocurine, and vecuronium, resistance to Nuromax, manifested by a reduced intensity and/or shortened duration of block, must be considered when Nuromax is selected for use in patients receiving phenytoin or carbamazepine (see **Drug Interactions** subsection of PRECAUTIONS).

As with other nondepolarizing neuromuscular blocking agents, a reduction in dosage of Nuromax must be considered in cachectic or debilitated patients, in patients with neuromuscular diseases, severe electrolyte abnormalities, or carcinomatosis, and in other patients in whom potentiation of neuromuscular block or difficulty with reversal is anticipated. Increased doses of Nuromax may be required in burn patients (see PRECAUTIONS).

INDICATIONS AND USAGE: Nuromax is a long-acting neuromuscular blocking agent, indicated as an adjunct to general anesthesia, to provide skeletal muscle relaxation during surgery. Nuromax can also be used to provide skeletal muscle relaxation for endotracheal intubation.

CONTRAINDICATIONS: Nuromax is contraindicated in patients known to have hypersensitivity to it.

WARNINGS: NUROMAX SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE WITHIN IMMEDIATE REACH. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING LONG-ACTING NEUROMUSCULAR BLOCKING AGENTS SUCH AS NUROMAX EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANTS, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

NUROMAX HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

Nuromax Injection is acidic (pH 3.9 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions).

Nuromax Injection contains benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. See **Pediatric Use** subsection of PRECAUTIONS.

PRECAUTIONS: General: Nuromax has no clinically significant effects on heart rate; therefore, Nuromax will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (e.g., carcinomatosis), the use of a peripheral nerve stimulator and a small test dose of Nuromax is recommended to assess the level of neuromuscular block and to monitor dosage requirements. Shorter acting muscle relaxants than Nuromax may be more suitable for these patients.

Resistance to nondepolarizing neuromuscular blocking agents may develop in patients with burns depending upon the time elapsed since the injury and the size of the burn. Nuromax has not been studied in patients with burns.

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Nuromax has not been studied in patients with asthma.

No data are available to support the use of Nuromax by intramuscular injection.

Renal and Hepatic Disease: Nuromax has been studied in patients with end-stage kidney (n=8) or liver (n=7) disease undergoing transplantation procedures (see CLINICAL PHARMACOLOGY). The possibility of prolonged neuromuscular block in patients undergoing renal transplantation and the possibility of a variable onset and duration of neuromuscular block in patients undergoing liver transplantation must be considered when Nuromax is used in such patients.

Obesity: Administration of Nuromax on the basis of actual body weight is associated with a prolonged duration of action in obese patients (patients weighing $\geq 30\%$ more than ideal body weight for height) (see CLINICAL PHARMACOLOGY). Therefore, the dose of Nuromax should be based upon ideal body weight in obese patients (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY).

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, Nuromax did not trigger MH. Nuromax has not been studied in MH-susceptible patients. Since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of Nuromax in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Prior administration of succinylcholine has no clinically important effect on the neuromuscular blocking action of Nuromax.

The use of Nuromax before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on concomitant use of Nuromax and other nondepolarizing neuromuscular blocking agents.

Isolurane, enflurane and halothane decrease the ED_{50} of Nuromax by 30% to 45%. These agents may also prolong the clinically effective duration of action by up to 25%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as Nuromax include certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quindine.

As with some other nondepolarizing neuromuscular blocking agents, the time of onset of neuromuscular block induced by Nuromax is lengthened and the duration of block is shortened in patients receiving phenytoin or carbamazepine.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Nuromax was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, in the mouse lymphoma assay, and in the human lymphocyte assay. In the *in vivo* rat bone marrow cytogenetic assay, statistically significant increases in the incidence of structural abnormalities, relative to vehicle controls, were observed in male rats dosed with 0.1 mg/kg (0.625 mg/m²) Nuromax and sacrificed at 6 hours, but not at 24 or 48 hours, and in female rats dosed with 0.2 mg/kg (1.25 mg/m²) Nuromax and sacrificed at 24 hours, but not at 6 or 48 hours. There was no increase in structural abnormalities in either male or female rats given 0.3 mg/kg (1.875 mg/m²) Nuromax and sacrificed at 6, 24, or 48 hours. Thus, the incidence of abnormalities in the *in vivo* rat bone marrow cytogenetic assay was not dose-dependent and, therefore, the likelihood that the observed abnormalities were treatment-related or clinically significant is low.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Teratology testing in nonventilated, pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of Nuromax revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of Nuromax in pregnant women. Because animal studies are not always predictive of human response and the doses used were subparalyzing, Nuromax should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of Nuromax during labor, vaginal delivery, or cesarean section has not been studied. It is not known whether Nuromax administered to the mother has immediate or delayed effects on the fetus. The duration of action of Nuromax exceeds the usual duration of operative obstetrics (cesarean section). Therefore, Nuromax is not recommended for use in patients undergoing C-section.

Nursing Mothers: It is not known whether Nuromax is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following Nuromax administration to a nursing woman.

Pediatric Use: Nuromax has not been studied in children below the age of 2 years. See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age.

Geriatric Use: Nuromax has been used in elderly patients, including patients with significant cardiovascular disease. In elderly patients the onset of maximum block is slower and the duration of neuromuscular block produced by Nuromax is more variable and, in some cases, longer than in young adult patients (see **Pharmacodynamics and Individualization of Dosages** subsections of CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS: The most frequent adverse effect of nondepolarizing blocking agents as a class consists of an extension of the pharmacological action beyond the time needed for surgery and anesthesia. This effect may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency and apnea which require manual or mechanical ventilation until recovery is judged to be clinically adequate (see OVERDOSAGE). Inadequate reversal of neuromuscular block from Nuromax is possible, as with all nondepolarizing agents. Prolonged neuromuscular block and inadequate reversal may lead to postoperative complications.

Observed in Clinical Trials: Adverse experiences were uncommon among the 1034 surgical patients and volunteers who received Nuromax and other drugs in U.S. clinical studies in the course of a wide variety of procedures conducted during balanced or inhalational anesthesia. The following adverse experiences were reported in patients administered Nuromax (all events judged by investigators during the clinical trials to have a possible causal relationship):

Incidence Greater than 1% - None

Incidence Less than 1% -

Cardiovascular:	hypotension, [*] flushing, [*] ventricular fibrillation, myocardial infarction
Respiratory:	bronchospasm, wheezing
Dermatological:	urticaria, injection site reaction
Special Senses:	diplopia
Nonspecific:	difficult neuromuscular block reversal, prolonged drug effect, fever

^{*} Reports of ventricular fibrillation (n=1) and myocardial infarction (n=1) were limited to ASA Class 3-4 patients undergoing cardiac surgery (n=142).

[†] 0.3% incidence. All other reactions unmarked were $\leq 0.1\%$.

OVERDOSAGE: Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (e.g., neostigmine, edrophonium) in conjunction with an appropriate anticholinergic agent (see **Antagonism of Neuromuscular Block**).

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCK. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED. T_4/T_1 SHOULD BE > 0.7 BEFORE ANTAGONISM IS ATTEMPTED.

In an analysis of patients in whom antagonism of neuromuscular block was evaluated following administration of single doses of neostigmine averaging 0.06 mg/kg (range: 0.05 to 0.075) administered at approximately 25% T_1 spontaneous recovery during balanced anesthesia, 71% of patients exhibited $T_4/T_1 \geq 0.7$ before monitoring was discontinued. For these patients, the mean time to $T_4/T_1 \geq 0.7$ was 19 minutes (range: 7 to 55). As with other long-acting nondepolarizing neuromuscular blocking agents, the time for recovery of neuromuscular function following administration of neostigmine is dependent upon the level of residual neuromuscular block at the time of attempted reversal; longer recovery times than those cited above may be anticipated when neostigmine is administered at more profound levels of block (i.e., at $< 25\%$ T_1 recovery).

Patients should be evaluated for adequate clinical evidence of antagonism, e.g., 5-second head lift, and grip strength. Ventilation must be supported until no longer required. As with other neuromuscular blocking agents, physicians should be alert to the possibility that the action of the drugs used to antagonize neuromuscular block may wear off before the effects of Nuromax on the neuromuscular junction have declined sufficiently.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see **Drug Interactions** subsection of PRECAUTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular block.

In clinical trials, a dose of 1 mg/kg edrophonium was not as effective as a dose of 0.06 mg/kg neostigmine in antagonizing moderate to deep levels of neuromuscular block (i.e., $< 60\%$ T_1 recovery). Therefore, the use of 1 mg/kg edrophonium is not recommended for reversal from moderate to deep levels of block. The use of pyridostigmine has not been studied.

DOSAGE AND ADMINISTRATION: NUROMAX SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

Nuromax, like other long-acting neuromuscular blocking agents, displays variability in the duration of its effect. The potential for a prolonged clinical duration of neuromuscular block must be considered when Nuromax is selected for administration. The dosage information provided below is intended as a guide only. Doses should be individualized (see **Individualization of Dosages** subsection of CLINICAL PHARMACOLOGY). Factors that may warrant dosage adjustment include: advancing age, the presence of kidney or liver disease, or obesity (patients weighing $\geq 30\%$ more than ideal body weight for height). The use of a peripheral nerve stimulator will permit the most advantageous use of Nuromax, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Adults: Initial Doses: When administered as a component of a thiopental/narcotic induction-intubation paradigm as well as for production of long-duration neuromuscular block during surgery, 0.05 mg/kg (2 x ED_{95}) Nuromax produces good-to-excellent conditions for tracheal intubation in 5 minutes in approximately 90% of patients. Lower doses of Nuromax may result in a longer time for development of satisfactory intubation conditions. Clinically effective neuromuscular block may be expected to last approximately 100 minutes on average (range: 39 to 232) following 0.05 mg/kg Nuromax administered to patients receiving balanced anesthesia.

An initial Nuromax dose of 0.08 mg/kg (3 x ED_{95}) should be reserved for instances in which a need for very prolonged neuromuscular block is anticipated. In approximately 90% of patients, good-to-excellent intubation conditions may be expected in 4 minutes after this dose; however, clinically effective block may be expected to persist for as long as 160 minutes or more (range: 110 to 338) (see CLINICAL PHARMACOLOGY).

If Nuromax is administered during steady-state isoflurane, enflurane, or halothane anesthesia, reduction of the Nuromax dose by one-third should be considered.

When succinylcholine is administered to facilitate tracheal intubation in patients receiving balanced anesthesia, an initial dose of 0.025 mg/kg (ED_{95}) Nuromax provides about 60 minutes (range: 9 to 145) of clinically effective neuromuscular block for surgery. For a longer duration of action, a larger initial dose may be administered.

Maintenance Doses: Maintenance dosing will generally be required about 60 minutes after an initial dose of 0.025 mg/kg Nuromax or 100 minutes after an initial dose of 0.05 mg/kg Nuromax during balanced anesthesia. Repeated maintenance doses administered at 25% T_1 recovery may be expected to be required at relatively regular intervals in each patient. The interval may vary considerably between patients. Maintenance doses of 0.005 and 0.01 mg/kg Nuromax each provide an average 30 minutes (range: 9 to 57) and 45 minutes (range: 14 to 108), respectively, of additional clinically effective neuromuscular block. For shorter or longer desired durations, smaller or larger maintenance doses may be administered.

Children: When administered during halothane anesthesia, an initial dose of 0.03 mg/kg (ED_{95}) produces maximum neuromuscular block in about 7 minutes (range: 5 to 11) and clinically effective block for an average of 30 minutes (range: 12 to 54). Under halothane anesthesia, 0.05 mg/kg produces maximum block in about 4 minutes (range: 2 to 10) and clinically effective block for 45 minutes (range: 30 to 80). Maintenance doses are generally required more frequently in children than in adults. Because of the potentiating effect of halothane seen in adults, a higher dose of Nuromax may be required in children receiving balanced anesthesia than in children receiving halothane anesthesia to achieve a comparable onset and duration of neuromuscular block. Nuromax has not been studied in children below the age of 2 years.

Compatibility: Y-site Administration: Nuromax Injection may not be compatible with alkaline solutions with a pH greater than 8.5 (e.g., barbiturate solutions).

Nuromax is compatible with:

- | | |
|--|--|
| • 5% Dextrose Injection USP | • 5% Dextrose and Lactated Ringer's Injection |
| • 0.9% Sodium Chloride Injection USP | • Sulfenta [®] (sulfentanil citrate) Injection, diluted as directed |
| • 5% Dextrose and 0.9% Sodium Chloride Injection USP | • Alfenta [®] (alfentanil hydrochloride) Injection, diluted as directed |
| • Lactated Ringer's Injection USP | • Sublimaze [®] (fentanyl citrate) Injection, diluted as directed |

Dilution Stability: Nuromax diluted up to 1:10 in 5% Dextrose Injection USP or 0.9% Sodium Chloride Injection USP has been shown to be physically and chemically stable when stored in polypropylene syringes at 5° to 25°C (41° to 77°F), for up to 24 hours. Since dilution diminishes the preservative effectiveness of benzyl alcohol, aseptic techniques should be used to prepare the diluted product. Immediate use of the diluted product is preferred, and any unused portion of diluted Nuromax should be discarded after 8 hours.

HOW SUPPLIED: Nuromax Injection, 1 mg doxacurium in each mL.

5 mL Multiple Dose vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS). Tray of 10 (NDC 0081-0763-44).

STORAGE: Store Nuromax Injection at room temperature of 15° to 25°C (59° to 77°F). DO NOT FREEZE.

U.S. Patent No. 4701460

- Emmott RS, Bracey BJ, Goldhill DR, Yate PM, Flynn PJ. Cardiovascular effects of doxacurium, pancuronium and vecuronium in anaesthetized patients presenting for coronary artery bypass surgery. *Br J Anaesth.* 1990;65:480-486.
- Tullock WC, Diana P, Cook DR, et al. Neuromuscular and cardiovascular effects of high-dose vecuronium. *Anesth Analg.* 1990;70:86-90.
- Stoops CM, Curtis CA, Kovach DA, et al. Hemodynamic effects of doxacurium chloride in patients receiving oxygen sufentanil anesthesia for coronary artery bypass grafting or valve replacement. *Anesthesiology.* 1988;69:365-370.



Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, NC 27709
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The Logical Choice



Crucial Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance. ¹	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance. ¹ ($P < .05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur. ¹⁻⁴	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma) ⁵
RECOVERY To 25% of control To 95% of control	25-45 min ³ 45-65 min ³	35-45 min ⁵ 60-70 min ⁵
DOSING FLEXIBILITY	The initial recommended dose is 0.08-0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects. ^{1,3,4}	Initial recommended dose is 0.4-0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P < .05$) and 0.6 mg/kg.* ^{2,5,6}
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature.† Can be reconstituted with various IV solutions including Lactated Ringers.‡	2-year shelf life under constant refrigeration.† Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated. ⁵

*Dose of atracurium above 0.5 mg/kg is not recommended.

‡Storage after reconstitution varies with solution. See package insert.

†As originally supplied by the respective manufacturers.

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.



ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it. **WARNINGS:** NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-esthetive surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation: Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations to patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypokalemic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia. C.M.S.C. Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intrathecal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxins B; colistin; and sodium colistide.

Other: Experience concerning injection of quinine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Feasible Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. Information presently available does not permit recommendations for use in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thioetherbarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (see PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thioetherbarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSEAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile

anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.06 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.25 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035	
0.8	0.008	0.0040	
0.9	0.009	0.0045	
1.0	0.010	0.0050	
1.1	0.011	0.0055	
1.2	0.012	0.0060	
1.3	0.013	0.0065	

*10 mg of Norcuron® in 100 mL solution

†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN		Patient Weight — kg							
Amount of Drug µg/kg/min	40	50	60	70	80	90	100		
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70		
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80		
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90		
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00		
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10		
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20		
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30		

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1/2 times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on usage in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children; therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEONATES. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

References

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- Kaufman JA, Dubois MY, Chen JC, Lea D. Pharmacodynamic effects of vecuronium: A dose response study. *J Clin Anesth*. 1989;1(6):434-439.
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ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

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H-3802



Roche Laboratories
a division of Hoffmann-La Roche Inc.

THE ADVANTAGE OF CO-INDUCTION

Anesthetic Synergy

VERSED first, followed by a second anesthetic

When given first, a small dose of VERSED® (midazolam HCl/Roche) may lower the induction ED₅₀ of barbiturates or narcotics up to 75%.¹⁻⁴ This synergistic effect appears to result from a mutual enhancement of binding-site affinity.¹⁻³ Clinically, co-induction may decrease toxicity and speed recovery.² VERSED can also abolish the excitatory effects and emergence phenomena associated with some induction agents,⁵ and its potent amnesic effect may avoid breakthrough awareness at times when short-acting induction agents may be wearing off.

- Allows lower doses of induction agents¹⁻⁵
- A smooth induction^{5,6}
- Less risk of breakthrough awareness^{5,6}
- A smooth emergence^{5,6}

Dosing considerations

As a standard precaution, prior to I.V. administration of VERSED in any dose, oxygen and resuscitative equipment should be immediately available. VERSED should be used as an induction agent only by persons trained in anesthesiology and who are familiar with all dosing and administration guidelines. Reduce dosage in elderly or debilitated patients, in patients receiving narcotic premedication and in those with limited pulmonary reserve.

It is recommended that patients do not drive or operate hazardous machinery after receiving VERSED until the effects of the drug (e.g., drowsiness) are gone or until the day after anesthesia. The decision must be individualized.

Please see summary of product information on following page.

INJECTABLE
VERSED®
midazolam HCl/Roche ^{IV}
FIRST

Injectable VERSED is available in
1 mg/mL and 5 mg/mL strengths.

References: 1. Tverskoy M, et al. Midazolam-thiopental anesthetic interaction in patients. *Anesth Analg*. 1988;67:342-345. 2. Vinik HR, Bradley EL Jr, Kissin I. Midazolam for collocation of thiopental anesthesia in patients. *Anesthesiology*. 1990; 73(3A):A1218. 3. Vinik HR, Bradley EL Jr, Kissin I. Midazolam-alfentanil synergism for anesthetic induction in patients. *Anesth Analg*. 1989;69:213-217. 4. Ben-Shiomi I, et al. Midazolam acts synergistically with fentanyl for induction of anaesthesia. *Br J Anaesth*. 1990;64:45-47. 5. White PF. Comparative evaluation of intravenous agents for rapid sequence induction — thiopental, ketamine, and midazolam. *Anesthesiology*. 1982;57:279-284. 6. Desiderio DP, Thorne AC. Awareness and general anaesthesia. *Acta Anaesthesiol Scand*. 1990;34(suppl 92):48-50.

VERSED® (brand of midazolam HCl/Roche)® INJECTION

Before prescribing, please consult complete product information, a summary of which follows:

Intravenous VERSED has been associated with respiratory depression and respiratory arrest, especially when used for conscious sedation. In some cases, where this was not recognized promptly and treated effectively, death or hypoxic encephalopathy has resulted. Intravenous VERSED should be used only in hospital or ambulatory care settings, including physicians' offices, that provide for continuous monitoring of respiratory and cardiac function. Immediate availability of resuscitative drugs and equipment and personnel trained in their use should be assured. (See WARNINGS.)

The initial intravenous dose for conscious sedation may be as little as 1 mg, but should not exceed 2.5 mg in a normal healthy adult. Lower doses are necessary for older (over 60 years) or debilitated patients and in patients receiving concomitant narcotics or other CNS depressants. The initial dose and all subsequent doses should never be given as a bolus; administer over at least 2 minutes and allow an additional 2 or more minutes to fully evaluate the sedative effect. The use of the 1 mg/mL formulation or dilution of the 5 mg/mL formulation is recommended to facilitate slower injection. Consult complete product information under DOSAGE AND ADMINISTRATION for complete dosing information.

CONTRAINDICATIONS: Patients with known hypersensitivity to the drug. Benzodiazepines are contraindicated in patients with acute narrow angle glaucoma; may be used in open angle glaucoma only if patients are receiving appropriate therapy.

WARNINGS: Never use without individualization of dosage. Prior to IV use in any dose, ensure immediate availability of oxygen, resuscitative equipment and skilled personnel for maintenance of a patent airway and support of ventilation. Continuously monitor for early signs of underventilation or apnea, which can lead to hypoxia/cardiac arrest unless effective countermeasures are taken immediately. Vital signs should continue to be monitored during the recovery period. Because IV VERSED depresses respiration, and opioid agonists and other sedatives can add to this depression, it should be administered as an induction agent only by a person trained in general anesthesia and should be used for conscious sedation only in the presence of personnel skilled in early detection of under-ventilation, maintaining a patent airway and supporting ventilation. For conscious sedation, do not administer IV by rapid or single bolus. Serious cardiorespiratory adverse events have occurred. These have included respiratory depression, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death. There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received VERSED. Hypotension occurred more frequently in the conscious sedation studies in patients premedicated with narcotic.

Reactions such as agitation, involuntary movements, hyperactivity and combative-ness have been reported. These may be due to inadequate or excessive dosing or improper administration; however, the possibility of cerebral hypoxia or true paradoxical reactions should be considered. Should these reactions occur, response to each dose of VERSED and all other drugs should be evaluated before proceeding. Concomitant use of barbiturates, alcohol or other CNS depressants may increase the risk of underventilation or apnea and may contribute to profound and/or prolonged drug effect. Narcotic premedication also depresses the ventilatory response to carbon dioxide stimulation.

Higher risk surgical, elderly or debilitated patients require lower dosages for induction of anesthesia, premedicated or not. Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of VERSED. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly. Because elderly patients frequently have inefficient function of one or more organ systems, and because dosage requirements have been shown to decrease with age, reduce initial dosage and consider possibility of a profound and/or prolonged effect.

Do not administer in shock, coma, acute alcohol intoxication with depression of vital signs. Particular care should be exercised in the use of IV VERSED in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances. Guard against unintended intra-arterial injection; hazards in humans unknown. Avoid extravasation.

Gross tests of recovery from the effects of VERSED cannot alone predict reaction time under stress. This drug is never used alone during anesthesia, and the contribution of other perioperative drugs and events can vary. The decision as to when patients may engage in activities requiring mental alertness must be individualized; it is recommended that no patient should operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided or until the day after anesthesia, whichever is longer.

Usage in Pregnancy: An increased risk of congenital malformations associated with the use of benzodiazepines (diazepam and chlordiazepoxide) has been suggested in several studies. If VERSED is used during pregnancy, apprise the patient of the potential hazard to the fetus.

PRECAUTIONS: General: Decrease intravenous doses in elderly and debilitated patients. These patients will also probably take longer to recover completely after VERSED for induction of anesthesia.

VERSED does not protect against increased intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anesthesia.

Information for patients: Communicate the following information and instructions to the patient when appropriate: 1. Inform your physician about any alcohol consumption and medicines you are now taking, including nonprescription drugs. Alcohol has an increased effect when consumed with benzodiazepines; therefore, caution should be exercised regarding simultaneous ingestion of alcohol and benzodiazepines.

VERSED® (brand of midazolam HCl/Roche)

2. Inform your physician if you are pregnant or are planning to become pregnant.

3. Inform your physician if you are nursing.

Drug Interactions: The sedative effect of IV VERSED is accentuated by premedication, particularly narcotics (e.g., morphine, meperidine, fentanyl) and also secobarbital and innovar (fentanyl and droperidol). Consequently, adjust the dosage according to the type and amount of premedication.

A moderate reduction in induction dosage requirements of thiopental (about 15%) has been noted following use of IM VERSED for premedication.

IV administration of VERSED decreases the minimum alveolar concentration (MAC) of halothane required for general anesthesia. This decrease correlates with the dose of VERSED administered.

Although the possibility of minor interactive effects has not been fully studied, VERSED and pancuronium have been used together in patients without noting clinically significant changes in dosage, onset or duration. VERSED does not protect against the characteristic circulatory changes noted after administration of succinylcholine or pancuronium, or against the increased intracranial pressure noted following administration of succinylcholine. VERSED does not cause a clinically significant change in dosage, onset or duration of a single intubating dose of succinylcholine. No significant adverse interactions with commonly used premedications or drugs used during anesthesia and surgery (including atropine, scopolamine, glycopyrrolate, diazepam, hydroxyzine, d-tubocurarine, succinylcholine and nondepolarizing muscle relaxants) or topical local anesthetics (including lidocaine, dyclonine HCl and Cetacaine) have been observed.

Drug/Laboratory test Interactions: Midazolam has not been shown to interfere with clinical laboratory test results.

Carcinogenesis, mutagenesis, impairment of fertility: Midazolam maleate was administered to mice and rats for two years. At the highest dose (80 mg/kg/day) female mice had a marked increase in incidence of hepatic tumors and male rats had a small but significant increase in benign thyroid follicular cell tumors. These tumors were found after chronic use, whereas human use will ordinarily be of single or several doses.

Midazolam did not have mutagenic activity in tests that were conducted.

A reproduction study in rats did not show any impairment of fertility at up to ten times the human IV dose.

Pregnancy: Teratogenic effects: Pregnancy Category D. See WARNINGS section.

Midazolam maleate injectable, at 5 and 10 times the human dose, did not show evidence of teratogenicity in rabbits and rats.

Labor and delivery: Use in obstetrics has not been evaluated. Because midazolam is transferred transplacentally and because other benzodiazepines given in the last weeks of pregnancy have resulted in neonatal CNS depression, VERSED is not recommended for obstetrical use.

Nursing mothers: It is not known whether midazolam is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when injectable VERSED is administered to a nursing woman.

Pediatric use: Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: See WARNINGS concerning serious cardiorespiratory events and possible paradoxical reactions. Fluctuations in vital signs following parenteral administration were the most frequently seen findings and included decreased tidal volume and/or respiratory rate decrease (23.3% of patients following IV and 10.8% of patients following IM administration) and apnea (15.4% of patients following IV administration), as well as variations in blood pressure and pulse rate.

Following IM injection: headache (1.3%); local effects at IM site: pain (3.7%), induration (0.5%), redness (0.5%), muscle stiffness (0.3%). Following IV administration: hiccoughs (3.9%), nausea (2.8%), vomiting (2.6%), coughing (1.3%), "oversedation" (1.6%), headache (1.5%), drowsiness (1.2%); local effects at the IV site: tenderness (5.6%), pain during injection (5.0%), redness (2.6%), induration (1.7%), phlebitis (0.4%). Other effects (<1%) mainly following IV administration: Respiratory:

Laryngospasm, bronchospasm, dyspnea, hyperventilation, wheezing, shallow respirations, airway obstruction, tachypnea. Cardiovascular: Bigeminy, premature ventricular contractions, vasovagal episode, tachycardia, nodal rhythm.

Gastrointestinal: Acid taste, excessive salivation, retching. CNS/Neuromuscular: Retrograde amnesia, euphoria, confusion, argumentativeness, nervousness, anxiety, grogginess, restlessness, emergence delirium or agitation, prolonged emergence from anesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, athetoid movements, ataxia, dizziness, dysphoria, slurred speech, dysphoria, paraesthesia. Special Senses: Blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, visual disturbance, difficulty focusing eyes, ears blocked, loss of balance, lightheadedness. Integumentary: Hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, rash, pruritus.

Miscellaneous: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma.

Drug Abuse and Dependence: Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

OVERDOSAGE: Manifestations would resemble those observed with other benzodiazepines (e.g., sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, untoward effects on vital signs). No specific organ toxicity would be expected.

DOSAGE AND ADMINISTRATION: VERSED is a potent sedative agent which requires slow administration and individualization of dosage. Clinical experience has shown VERSED to be 3 to 4 times as potent per mg as diazepam.

BECAUSE SERIOUS AND LIFE-THREATENING CARDIORESPIRATORY ADVERSE EVENTS HAVE BEEN REPORTED, PROVISION FOR MONITORING, DETECTION AND CORRECTION OF THESE REACTIONS MUST BE MADE FOR EVERY PATIENT TO WHOM VERSED INJECTION IS ADMINISTERED, REGARDLESS OF AGE OR HEALTH STATUS. Excess doses or rapid or single bolus intravenous administration may result in respiratory depression and/or arrest. (See WARNINGS.) Prior to use refer to the DOSAGE AND ADMINISTRATION section in the complete product information.

P.1 0988



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Precise Control



Precise Hands

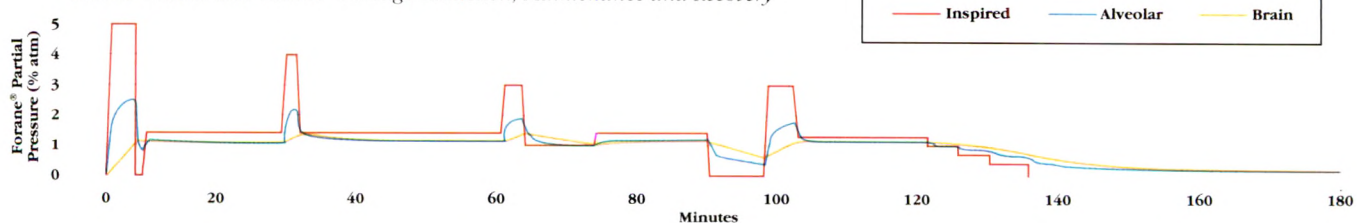
Before Surgical Incision

Overpressuring* with Forane® rapidly achieves the desired anesthetic tension in the brain, giving you confidence that your patient is ready for surgery.

During Maintenance

Alveolar concentrations of Forane® are easily monitored and adjusted to accommodate your patient's changing anesthetic requirements.

Precise Control with Forane® Through Induction, Maintenance and Recovery



*Overpressuring requires the use of an inspired concentration that can cause cardiovascular depression if administered for a sufficient period of time. Thus, the anesthetist must closely monitor blood pressure and heart rate during the period overpressure is used.

Graph generated from a computer simulation,[†] depicting the relationship between inspired, alveolar and brain partial pressures throughout a surgical procedure. During maintenance, brief periods of overpressure are used to accommodate the patient's changing anesthetic requirements during times of increased surgical stimulation.

[†] GUS Computer Simulation. GUS is a registered trademark of Quincy Street Corporation, Phoenix, AZ.



-On Control

Upon Recovery

Precise control of anesthetic depth and rapid elimination of Forane® through the lungs facilitate an uneventful postanesthetic course for your patient.

Please refer to Prescribing Information on the following page.



Forane®
(isoflurane, USP)

Precise Hands-On Control

Anaquest





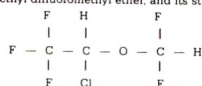
Forane® (isoflurane, USP)

Precise Hands-On Control

CAUTION Federal Law Prohibits Dispensing without Prescription

DESCRIPTION

FORANE (isoflurane, USP) a nonflammable liquid administered by vaporizing, is a general inhalation anesthetic drug. It is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether, and its structural formula is:



Some physical constants are:

Molecular weight	184.5
Boiling point at 760 mm Hg	48.5 °C (uncorr.)
Refractive index n_D^{20}	1.2990/3005
Specific gravity 25 °/25 °C	1.496
Vapor pressure in mm Hg**	20 °C 238 25 °C 295 30 °C 367 35 °C 450

**Equation for vapor pressure calculation:

$$\log_{10} P_{\text{vap}} = A + \frac{B}{T} \quad \text{where: } A = 8.056, B = -1664.58, T = \text{°C} + 273.16 \text{ (Kelvin)}$$

Partition coefficients at 37 °C

Water/gas	0.61
Blood/gas	1.43
Oil/gas	90.8

Partition coefficients at 25 °C: rubber and plastic

Conductive rubber/gas	62.0
Butyl rubber/gas	75.0
Polyvinyl chloride/gas	110.0
Polyethylene/gas	~2.0
Polyurethane/gas	~1.4
Polyolefin/gas	~1.1
Butyl acetate/gas	~2.5
Purity by gas chromatography	>99.9%

Lower limit of flammability in oxygen or nitrous oxide at 9 joules/sec and 23 °

None

Lower limit of flammability in oxygen or nitrous oxide at 900 joules/sec and 23 °

Greater than useful concentration in anesthesia

Isoflurane is a clear, colorless, stable liquid containing no additives or chemical stabilizers. Isoflurane has a mildly pungent, musty, etheral odor. Samples stored in indirect sunlight in clear, colorless glass for five years, as well as samples directly exposed for 30 hours to a 2 amp, 115 volt, 60 cycle long wave UV light were unchanged in composition as determined by gas chromatography. Isoflurane in one normal sodium methoxide-methanol solution, a strong base, for over six months consumed essentially no alkali, indicative of strong base stability. Isoflurane does not decompose in the presence of soda lime, and does not attack aluminum, tin, brass, iron or copper.

CLINICAL PHARMACOLOGY

FORANE (isoflurane, USP) is an inhalation anesthetic. The MAC (minimum alveolar concentration) in man is as follows:

Age	100% Oxygen	70% N ₂ O
26 ± 4	1.28	0.56
44 ± 7	1.15	0.50
64 ± 5	1.05	0.37

Induction of and recovery from isoflurane anesthesia are rapid. Isoflurane has a mild pungency which limits the rate of induction, although excessive salivation or tracheobronchial secretions do not appear to be stimulated. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia may be changed rapidly with isoflurane. Isoflurane is a profound respiratory depressant. RESPIRATION MUST BE MONITORED CLOSELY AND SUPPORTED WHEN NECESSARY. As anesthetic dose is increased, tidal volume decreases and respiratory rate is unchanged. This depression is partially reversed by surgical stimulation, even at deeper levels of anesthesia. Isoflurane evokes a sigh response reminiscent of that seen with diethyl ether and enflurane, although the frequency is less than with enflurane.

Blood pressure decreases with induction of anesthesia but returns toward normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding decreases in blood pressure. Nitrous oxide diminishes the inspiratory concentration of isoflurane required to reach a desired level of anesthesia and may reduce the arterial hypotension seen with isoflurane alone. Heart rhythm is remarkably stable. With controlled ventilation and normal PaCO₂, cardiac output is maintained despite increasing depth of anesthesia primarily through an increase in heart rate which compensates for a reduction in stroke volume. The hypercapnia which attends spontaneous ventilation during isoflurane anesthesia further increases heart rate and raises cardiac output above awake levels. Isoflurane does not sensitize the myocardium to exogenously administered epinephrine in the dog. Limited data indicate that subcutaneous injection of 0.25 mg of epinephrine (50 mL of 1,200,000 solution) does not produce an increase in ventricular arrhythmias in patients anesthetized with isoflurane.

Muscle relaxation is often adequate for intra-abdominal operations at normal levels of anesthesia. Complete muscle paralysis can be attained with small doses of muscle relaxants. ALL COMMONLY USED MUSCLE RELAXANTS ARE MARKEDLY POTENTIATED WITH ISOFLURANE, THE EFFECT BEING MOST PROFOUND WITH THE NONDEPOLARIZING TYPE. Neostigmine reverses the effect of nondepolarizing muscle relaxants in the presence of isoflurane. All commonly used muscle relaxants are compatible with isoflurane.

Isoflurane can produce coronary vasodilation at the arteriolar level in selected animal models^{1,2}; the drug is probably also a coronary dilator in humans. Isoflurane, like some other coronary arteriolar dilators, has been shown to divert blood from collateral dependent myocardium to normally perfused areas in an animal model ("coronary steal"). Clinical studies to date evaluating myocardial ischemia, infarction and death as outcome parameters have not established that the coronary arterial dilating property of isoflurane is associated with coronary steal or myocardial ischemia in patients with coronary artery disease.^{3,5,6,7}

Pharmacokinetics: Isoflurane undergoes minimal biotransformation in man. In the postanesthesia period, only 0.17% of the isoflurane taken up can be recovered as urinary metabolites.

INDICATIONS AND USAGE

FORANE (isoflurane, USP) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Known sensitivity to FORANE (isoflurane, USP) or to other halogenated agents.

Known or suspected genetic susceptibility to malignant hyperthermia.

WARNINGS

Since levels of anesthesia may be altered easily and rapidly, only vaporizers producing predictable concentrations should be used. Hypotension and respiratory depression increase as anesthesia is deepened.

Increased blood loss comparable to that seen with halothane has been observed in patients undergoing abortions. FORANE (isoflurane, USP) markedly increases cerebral blood flow at deeper levels of anesthesia. There may be a transient rise in cerebral spinal fluid pressure which is fully reversible with hyperventilation.

PRECAUTIONS

General: As with any potent general anesthetic, FORANE (isoflurane, USP) should only be administered in an adequately equipped anesthetizing environment by those who are familiar with the pharmacology of the drug and qualified by training and experience to manage the anesthetized patient.

Regardless of the anesthetics employed, maintenance of normal hemodynamics is important to the avoidance of myocardial ischemia in patients with coronary artery disease.^{4,5,6,7}

Information to Patients: Isoflurane, as well as other general anesthetics, may cause a slight decrease in intellectual function for 2 or 3 days following anesthesia. As with other anesthetics, small changes in moods and symptoms may persist for up to 6 days after administration.

Laboratory Tests: Transient increases in BSP retention, blood glucose and serum creatinine with decrease in BUN, serum cholesterol and alkaline phosphatase have been observed.

Drug Interactions: Isoflurane potentiates the muscle relaxant effect of all muscle relaxants, most notably nondepolarizing muscle relaxants, and MAC (minimum alveolar concentration) is reduced by concomitant administration of N₂O. See CLINICAL PHARMACOLOGY.

Carcinogenesis: Swiss ICR mice were given isoflurane to determine whether such exposure might induce neoplasia. Isoflurane was given at 1/2, 1/8 and 1/32 MAC for four in-utero exposures and for 24 exposures to the pups during the first nine weeks of life. The mice were killed at 15 months of age. The incidence of tumors in these mice was the same as in untreated control mice which were given the same background gases, but not the anesthetic.

Pregnancy Category C: Isoflurane has been shown to have a possible anesthetic related fetotoxic effect in mice when given in doses 6 times the human dose. There are no adequate and well-controlled studies in pregnant women. Isoflurane should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when isoflurane is administered to a nursing woman.

Malignant Hyperthermia: In susceptible individuals, isoflurane anesthesia may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. The syndrome includes nonspecific features such as muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and unstable blood pressure. (It should also be noted that many of these nonspecific signs may appear with light anesthesia, acute hypoxia, etc.) An increase in overall metabolism may be reflected in an elevated temperature (which may rise rapidly early or late in the case, but usually is not the first sign of augmented metabolism) and an increased usage of the CO₂ absorption system (hot canister). PaO₂ and pH may decrease, and hyperkalemia and a base deficit may appear. Treatment includes discontinuance of triggering agents (e.g., isoflurane), administration of intravenous dantrolene sodium, and application of supportive therapy. Such therapy includes vigorous efforts to restore body temperature to normal, respiratory and circulatory support as indicated, and management of electrolyte-fluid-acid-base derangements. (Consult prescribing information for dantrolene sodium intravenous for additional information on patient management.) Renal failure may appear later, and urine flow should be sustained if possible.

ADVERSE REACTIONS

Adverse reactions encountered in the administration of FORANE (isoflurane, USP) are in general dose dependent extensions of pharmacophysiological effects and include respiratory depression, hypotension and arrhythmias.

Shivering, nausea, vomiting and ileus have been observed in the postoperative period.

As with all other general anesthetics, transient elevations in white blood count have been observed even in the absence of surgical stress.

See PRECAUTIONS for information regarding malignant hyperthermia.

OVERDOSAGE

In the event of overdosage, or what may appear to be overdosage, the following action should be taken:

Stop drug administration, establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

DOSEAGE AND ADMINISTRATION

Premedication: Premedication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by FORANE (isoflurane, USP) and the heart rate tends to be increased. The use of anticholinergic drugs is a matter of choice.

Inspired Concentration: The concentration of isoflurane being delivered from a vaporizer during anesthesia should be known. This may be accomplished by using:

- vaporizers calibrated specifically for isoflurane,
- vaporizers from which delivered flows can be calculated, such as vaporizers delivering a saturated vapor which is then diluted. The delivered concentration from such a vaporizer may be calculated using the formula:

$$\% \text{ isoflurane} = \frac{100 P_V F_V}{F_T (P_A - P_V)}$$

where:

- P_A = Pressure of atmosphere
- P_V = Vapor pressure of isoflurane
- F_V = Flow of gas through vaporizer (mL/min)
- F_T = Total gas flow (mL/min)

Isoflurane contains no stabilizer. Nothing in the agent alters calibration or operation of these vaporizers.

Induction: Induction with isoflurane in oxygen or in combination with oxygen-nitrous oxide mixtures may produce coughing, breath holding, or laryngospasm. These difficulties may be avoided by the use of a hypnotic dose of an ultra-short acting barbiturate. Inspired concentrations of 1.5 to 3.0% isoflurane usually produce surgical anesthesia in 7 to 10 minutes.

Maintenance: Surgical levels of anesthesia may be sustained with a 1.0 to 2.5% concentration when nitrous oxide is used concomitantly. An additional 0.5 to 1.0% may be required when isoflurane is given using oxygen alone. If added relaxation is required, supplemental doses of muscle relaxants may be used.

The level of blood pressure during maintenance is an inverse function of isoflurane concentration in the absence of other complicating problems. Excessive decreases may be due to depth of anesthesia and in such instances may be corrected by lightening anesthesia.

HOW SUPPLIED

FORANE (isoflurane, USP), NDC 10019-360-40, is packaged in 100 mL amber-colored bottles.

Storage: Store at room temperature 15 ° - 30 °C (59 ° - 86 °F). Isoflurane contains no additives and has been demonstrated to be stable at room temperature for periods in excess of five years.

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Editorial: The Big "Little Problem"

Patricia A. Kapur, MD

Department of Anesthesiology, University of California, Los Angeles, California

Perioperative nausea and emesis pose problems for patients undergoing all types of procedures requiring anesthesia or sedation. Particular groups of patients have been identified as being at higher risk, i.e., those with predisposing factors to prolonged gastric emptying (e.g., obstetric, bowel obstruction, or diabetic), those with recent food or liquid intake, those with inadequate protective mechanisms (e.g., hiatal hernia, nasogastric tube in place, or anesthetized upper airway), or those undergoing nausea-producing procedures, such as laparoscopy. As the authors of the accompanying articles (1,2) have pointed out, previous pharmacologic efforts to diminish the incidence and/or reduce the risk of emesis have included administering antihistaminics, anticholinergics, and dopamine antagonists. Sometimes narcotic-based anesthetic techniques are avoided. Physical maneuvers have included imposing various "nothing per os" regimens, preanesthetic suctioning of gastric contents, application of cricoid cartilage pressure, avoiding inflation of the stomach during ventilation by mask, and ingestion of antacid solutions. None of the above, alone or in combination, have been entirely successful in mitigating the distressing occurrence of emesis and its potential sequelae.

The predisposing factors mentioned above are more common within the inpatient population. However, as the number of acceptable surgical procedures increases in the field of ambulatory anesthesia, the need to find more effective alternatives to the options now available becomes more urgent. The potential cost savings of performing these procedures on an ambulatory basis may be negated by an unanticipated postoperative admission for intractable nausea (3). In addition, although intractable nausea is distressing, possibly dehydrating, and not easily manageable at home, the expense of a hospital stay is disproportionate to the actual morbidity of nausea for most healthy outpatients. Thus the therapy of last resort, hospital-

ization, is ultimately unsatisfactory for the patient, the anesthesiologist, and the surgeon.

Even lesser degrees of postoperative nausea are often perceived as failures of therapy, rather than as an unavoidable consequence of the perioperative experience. In most instances, the latter is in fact the case because of imperfect treatment options. When queried about previous anesthetic experiences, many patients are heard to lament about the distressing nausea after a prior procedure and beg to be spared that experience again. During preoperative evaluations for subsequent anesthetics, such patients are often assured that the latest available antiemetic medications will be administered and that a nausea-sparing anesthetic technique will be used. However, anesthesia providers cannot be sure that such a goal will be realized with the antiemetic treatment alternatives now available.

A potential new entry into the antiemetic pharmacopeia is ondansetron, of the class of selective 5-hydroxytryptamine subtype 3 (5-HT₃) receptor antagonists, which lack effects at cholinergic, adrenergic, dopaminergic, or histaminergic receptors (4). Ondansetron (\pm 1,2,3,9-tetrahydro-9-methyl-3[(2-methyl-1H-imidazol)-1-methyl]-4H-carbazol-4-one, monohydrochloride, dihydrate) is structurally related to serotonin. 5-HT₃ receptors are located both peripherally (vagal nerve terminals) and centrally (chemoreceptor trigger zone). The antiemetic properties of ondansetron may be mediated peripherally, centrally, or both.

Ondansetron has been studied in relation to cancer chemotherapy-induced emesis (5,6), which is associated with serotonin release from small intestine enterochromaffin cells and urinary excretion of serotonin metabolites. Presumably, the release of serotonin stimulates vagal afferent 5-HT₃ receptors and/or the central vomiting reflex. In experimental animal studies, cisplatin-induced emesis can be prevented by section of the abdominal vagus and greater splanchnic nerve, or by pretreatment with either a serotonin synthesis inhibitor or a 5-HT₃ receptor antagonist. In normal volunteers, ondansetron has little effect on lower esophageal sphincter pressure, esophageal or gastric motility, or small bowel transit time. By 5-HT₃ selectivity, the undesirable side effects of using an-

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Address correspondence to Dr. Kapur, Department of Anesthesiology, University of California, Los Angeles, 10833 Le Conte Avenue, Los Angeles, CA 90024-1778.

tagonists of dopaminergic, cholinergic, or histaminergic receptors as antiemetic agents, such as dysphoria, sedation, or extrapyramidal symptoms, will presumably be avoided. Ondansetron is hepatically metabolized, with a half-life of 3–5 h in healthy volunteers. Clearance decreases and half-life increases with increasing age. There was no difference, however, in the prevention of nausea and emesis in pediatric chemotherapy patients over 4 yr of age or in elderly patients in trials to date (7).

Based on the success of ondansetron in the treatment of cytotoxic chemotherapy-induced emesis, several groups describe the clinical application of ondansetron to the treatment of postoperative nausea and vomiting. In a study published in the June 1991 issue of *Anesthesia and Analgesia*, Leeser and Lip (8) found that the preoperative administration of ondansetron, 16 mg orally, reduced the incidence of postoperative nausea and vomiting from 52% and 40% (i.e., placebo) to 17% and 12%, respectively, in patients undergoing abdominal gynecologic operations. The accompanying two articles (1,2) also report clinical applications of ondansetron to the treatment of postoperative nausea and vomiting. Larijani et al. (1), compared a single intravenous dose of 8 mg of ondansetron with placebo in a randomized, double-blind scheme, for the treatment of nausea or vomiting within 2 h of a thiopental-N₂O-narcotic-muscle relaxant anesthetic in a unselected group of 36 inpatients (18 received each treatment). The 36 patients represented a 16% incidence of nausea and vomiting out of a total of 229 patients who consented to participate in the study. Success was defined as no requirement for a prochlorperazine rescue treatment because of abatement of nausea by 10 min after study drug administration as well as no vomiting. Twenty-eight percent of ondansetron-treated patients and 78% of placebo-treated patients failed these criteria. Arterial blood pressure, heart rate, and respiratory rate were stable during the study; side effects were minor and questionably related to the treatments, according to the authors.

Bodner and White (2) looked at a more homogeneous group of young female patients undergoing outpatient laparoscopic gynecologic procedures, again using a narcotic-based anesthetic technique (thiopental-alfentanil-succinylcholine-N₂O), in a randomized, double-blind, placebo-controlled design. Forty-six percent of 155 patients met the criteria for study drug administration, i.e., nausea lasting greater than 10 min or at least two episodes of emesis or retching in the recovery room. Of these, 35 received ondansetron (8 mg IV), and 36 received placebo. Those who were still nauseated 30 min after receiving the study drug, or who vomited, were given a rescue treatment consisting of metoclopra-

mid-hydroxyzine. A second rescue treatment with droperidol was also available. Noninvasive vital signs were stable, and side effects were minor and similar in number between the two groups. Forty-three percent of the ondansetron group received a first rescue treatment vs 86% of the placebo group. Forty-two percent of the placebo group who received metoclopramide-hydroxyzine met the treatment failure criteria and received a subsequent droperidol rescue treatment.

These three studies (1,2,8) clearly represent initial investigations in determining the suitability of ondansetron for the treatment of perioperative nausea and emesis. The difference in occurrence of nausea and emesis resulting in entry into the treatment wing of each study (16% Larijani et al. [1] vs 46% Bodner and White [2]) presumably reflects the high incidence of these sequelae in laparoscopic patients. In contrast to the Leeser and Lip (8) study, these two studies used ondansetron only for the treatment of established nausea and emesis, rather than prophylactically for the prevention of its occurrence. All three studies gave only one dose based on information in cancer patients (for whom it is recommended to receive ondansetron in three divided doses over the course of the day in which the chemotherapeutic agents are administered [6]). None of the studies were designed to compare ondansetron with other currently available perioperative antiemetic therapies. Although an inference can be drawn from the Bodner and White study (2) in which 43% of the ondansetron- and 42% of the placebo/metoclopramide-hydroxyzine-treated patients required other subsequent antiemetic treatment, the optimum dose of ondansetron is not known for this application, and the circumstances of the administration of ondansetron vs metoclopramide-hydroxyzine were not equivalent in the study. Finally, the role of a 5-HT₃ receptor antagonist in combination with other antiemetic agents with different mechanisms of action will need to be evaluated to determine (a) if additional efficacy can be obtained by drug combinations, (b) if drug doses can be lowered should combinations prove efficacious, and (c) that no untoward side effects occur with antiemetic combinations that include ondansetron.

Thus, although there is reason to be hopeful, it is too early to tell whether ondansetron will prove to be a significant improvement over extant therapies for the vexing problem of perioperative nausea and emesis. As compared with specific cytotoxic chemotherapeutic agents that trigger 5-HT release, perioperative nausea and emesis may be a multifactorial issue, related to a variety of physical, anatomic, physiologic, and pharmacologic interactions. On the other hand, despite a variety of etiologic factors in the

perioperative period, it is possible that ondansetron, alone or in combination with other agents with different mechanisms of action, may increase the probability of preventing or aborting nausea and emesis in perioperative patients.

Future studies with ondansetron, as well as with other potentially novel antiemetic agents, will be eagerly awaited. The impact and applicability of a significant improvement in antiemetic therapy for surgical patients would be enormous.

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Treatment of Postoperative Nausea and Vomiting With Ondansetron: A Randomized, Double-Blind Comparison With Placebo

Ghassem E. Larijani, PharmD, Irwin Gratz, DO, Mary Afshar, PharmD, and Shahab Minassian, MD

Departments of Anesthesiology, Obstetrics and Gynecology, and Pharmacology, Medical College of Pennsylvania, Philadelphia, Pennsylvania

Postoperative nausea and vomiting are common after recovery from general anesthesia. The antiemetic effect and safety of ondansetron, a selective serotonin type 3 (5-HT₃) receptor antagonist, was determined in 36 patients suffering from nausea or vomiting during recovery from intravenous anesthesia by giving either a single intravenous dose of ondansetron (8 mg, *n* = 18) or placebo (*n* = 18) over 2–5 min in a randomized, double-blind manner. A "rescue" antiemetic was provided in case of continued vomiting or at the patient's request. Antiemetic efficacy was defined as no request for rescue antiemetic and/or no vomiting episode during the next 4 h. There was no

significant difference in the demographic data between the groups. Administration of ondansetron or placebo had no significant effect on vital signs. Ondansetron was an effective antiemetic in 78% (14/18) and placebo was effective in 28% (5/18) of the patients. Laboratory studies 24 h later showed no signs of hematologic, hepatic, or renal alterations. Ondansetron at a dose of 8 mg administered intravenously over 2–5 min appears to be a safe and effective antiemetic for the treatment of nausea and/or vomiting after intravenous anesthesia.

(Anesth Analg 1991;73:246–9)

Nausea and vomiting are common during recovery from general anesthesia. In the absence of a perioperative antiemetic, 20%–40% of adult patients recovering from general anesthesia may experience postoperative emesis (1,2). The frequency of postoperative emesis is influenced by factors such as the patient's age and sex, type of surgery, duration of the surgical procedure, anesthetic technique, and the patient's ambulatory status (1–4). Although various antiemetics have been evaluated for the management of postoperative nausea and vomiting, none have proved to be uniformly effective and some have undesirable side effects (1–8).

The role of serotonin receptors in drug-induced emesis has recently received increasing attention. Drugs that competitively antagonize the effect of serotonin at 5-hydroxytryptamine subtype 3 (5-HT₃) receptors are useful antiemetics both in animals and in humans receiving cisplatin. Ondansetron, a 5-HT₃

receptor antagonist, is an effective antiemetic when used for the prevention of chemotherapy-induced nausea and vomiting (9–13). We designed this study to evaluate the efficacy and safety of ondansetron in the treatment of patients suffering from postoperative nausea and/or vomiting.

Methods

After explaining the nature of the study, written informed consent was obtained from ASA physical status I–III patients scheduled to undergo elective surgical procedures under general anesthesia. Patients between the ages of 18 and 65 yr were eligible. Exclusion criteria were laboratory or clinical evidence of renal, hematologic, or hepatic abnormalities, pregnancy, morbid obesity, a history of substance abuse, or antiemetic therapy within 24 h of surgery. Patients were premedicated with an intramuscular injection of morphine (5–10 mg) and atropine (1 mg) or scopolamine (0.4 mg) 1–2 h before induction of anesthesia. An intravenous anesthetic technique was used for all patients which consisted of thiopental, N₂O/O₂ (70/30 ratio), a narcotic (either morphine, fentanyl, sufentanil, or alfentanil), and a muscle relaxant (either pan-

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Address correspondence to Dr. Larijani, Department of Anesthesiology, The Medical College of Pennsylvania, 3300 Henry Avenue, Philadelphia, PA 19129.

curonium, vecuronium, atracurium, succinylcholine or *d*-tubocurarine). The choice of narcotic and muscle relaxant was left to the discretion of the attending anesthesiologist. No patient received any antiemetic during the operation.

After arrival in the recovery room, patients were monitored according to the hospital protocol. Recovery room nurses knew the nature of the study and informed the study personnel if the patient complained of nausea or had a vomiting episode within 2 h of arrival in the recovery room. Patients who complained of nausea or vomited were asked to grade the severity of their nausea as none, mild, moderate, or severe. Patients who were nauseated and needed an antiemetic were then given either an intravenous injection of ondansetron (8 mg) diluted to 20 mL with normal saline or placebo over 2–5 min in a randomized, double-blind manner. Arterial blood pressure and heart rate were measured noninvasively immediately before and 2, 4, 6, 8, 10, 20, and 30 min after the injection. Respiratory rate was also measured at these times. If the nausea persisted for more than 10 min after injection or if vomiting occurred, then "rescue" antiemetic (intravenous prochlorperazine, 2–5 mg) was given and the patient was dropped from further antiemetic efficacy evaluation. Patients assessed the severity of nausea every 30 min for 4 h after administration of the study drug injection.

After the 4-h observation period, the antiemetic requirement of the patients was at the discretion of their primary care physician. Patients were given morphine or meperidine for postoperative pain. Blood samples for evaluation of renal, hepatic, and hematologic function were drawn 24 h after injection of ondansetron or placebo. Totally effective antiemetic response was defined as no request for rescue antiemetic and no further vomiting during the 4-h observation period. The study was approved by our institutional review board for the protection of human subjects.

Patients were randomized using a computer-generated randomization schedule provided by the Department of Biostatistics at Glaxo Inc. Data were analyzed by unpaired Student's *t*-test, Mantel-Haenszel χ^2 test, and two-way repeated measures analysis of variance followed by Duncan multiple range test. A *P* value <0.05 was considered significant. A 95% confidence interval using *t*-distribution is also reported. Data are reported as mean \pm SD.

Results

Two hundred twenty-nine patients (68 male, 161 female) gave informed consent to participate in this study and 50 (21.8%) of these patients (5 male, 45

Table 1. Demographic Data

Characteristics	Ondansetron	Placebo
No. of patients	18	18
Sex		
Male	1	1
Female	17	17
Ethnic origin		
White	13	12
Black	4	6
Oriental	1	0
Age (yr) ^a	35 \pm 10	37 \pm 7
Weight (kg) ^a	69 \pm 17	69 \pm 14.6
Height (cm) ^a	165 \pm 8	166 \pm 7.2

^aMean \pm SD.

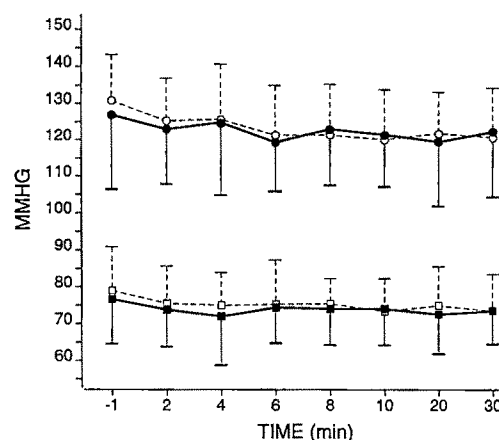


Figure 1. Arterial blood pressures (systolic, circles; diastolic, squares) after ondansetron (filled symbols) and placebo (open symbols) administration. Vertical lines represent 1 SD.

female) became nauseated or vomited within 2 h of arriving in the recovery room. Of these 50 patients, 14 either did not require antiemetic therapy or were no longer nauseated after the emetic episode. Thirty-six patients (2 male, 34 female) (15.7%) were given either ondansetron (*n* = 18) or placebo (*n* = 18).

Table 1 summarizes the demographic data. The majority of patients in each treatment group had undergone either an orthopedic or a gynecologic procedure. The two groups were not significantly different with respect to the patient demographics. The mean time between arrival in the recovery room and the administration of study drug was 37.4 ± 38 min in the ondansetron group and 33.2 ± 29.7 min in the placebo group.

Figure 1 depicts arterial blood pressures in the two treatment groups. There were no significant differences in heart rate, blood pressure, or respiratory rate between the two treatment groups during the course of the study. Within 2–4 min after the administration of placebo or ondansetron, systolic blood pressure

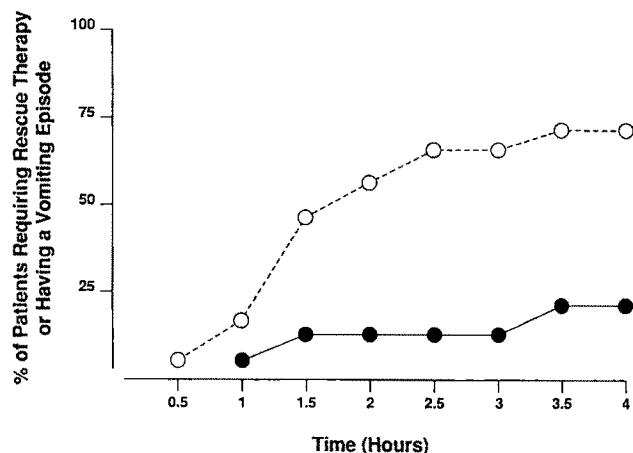


Figure 2. Percentage of the patients requiring rescue therapy or having a vomiting episode after study drug administration. ○, placebo; ●, ondansetron.

decreased by an average of approximately 5 mm Hg, diastolic blood pressure decreased by an average of 3 mm Hg, and heart rate decreased by an average of 4 beats/min.

There was no significant difference between the two treatment groups in the degree of nausea before treatment. Figure 2 depicts percentage of the patients requiring rescue therapy or having a vomiting episode as a function of time in the two groups. During the 4-h observation period, 12 of the 18 patients given placebo injection requested rescue therapy and one vomited. In the ondansetron group, three patients requested rescue therapy and one vomited. Control of nausea was obtained in significantly more patients given ondansetron than in patients given placebo injections (78% vs 28%, $P < 0.01$, 95% confidence interval = 22%–78%). No significant difference in the nausea score could be demonstrated between the two treatment groups during the course of the study. The mean time from the administration of the study drug until the administration of rescue therapy was 92.2 ± 64.8 and 95.7 ± 86.4 min in the placebo and ondansetron groups, respectively.

There were no clinically significant changes in hematologic, hepatic, or renal data in either group. Adverse events were reported by five ondansetron-treated patients and one placebo-treated patient. In the ondansetron group adverse events included diplopia (1), rash (1), pruritus (1), and dizziness (3). The relationship between these side effects and ondansetron administration was assessed to be unlikely ($n = 3$) or unrelated ($n = 3$). In the group receiving placebo, one patient complained of dizziness.

Discussion

Postoperative nausea and vomiting are common sequelae of general anesthesia and a leading cause of

delayed discharge or hospital readmission after ambulatory surgical procedures (1,2,14). In the absence of a prophylactic antiemetic, the incidence of nausea and vomiting in an adult surgical population receiving general anesthesia is approximately 20%–40%, most of which occurs during the first 2 h of recovery from anesthesia (1,2). In patient populations such as those undergoing laparoscopic procedures, however, nausea and/or vomiting may occur more frequently during the first postoperative day (5). The incidence of nausea and vomiting during the first 2 h of surgery in our patient population, approximately 22%, was more frequent in young to middle-aged female patients, as has also been reported in other studies (1,2).

Various antiemetics have been evaluated for the prevention and/or treatment of postoperative nausea and vomiting. Despite a wide variation in response to antiemetics and associated undesired side effects, antiemetics are routinely used perioperatively (1–8). Ondansetron (GR 38032F) is a potent and highly selective antagonist of serotonin at the 5-HT₃ receptor with demonstrated antiemetic effect in animals and patients receiving cisplatin, other chemotherapy, or radiation therapy (9–13). The patient population selected in this study consisted of otherwise healthy patients expected to remain hospitalized for at least the first postoperative day, so that a more complete evaluation of the safety of ondansetron profiles could be made. The 8-mg dose of ondansetron selected for this study was based on its efficacy in cancer patients receiving high-dose cisplatin (>100 mg/m²) (15).

Although ondansetron was a significantly more effective antiemetic than a placebo injection in this study, no significant differences in the nausea score could be demonstrated between the two treatment groups during the course of the study. This is most likely due to the number of dropouts in the placebo group and/or perhaps the lack of sensitivity of a discrete scale in evaluating the subjective symptoms of nausea. The side effects observed in this study were relatively mild and judged to be either unrelated or not likely due to ondansetron administration. We conclude that ondansetron at a dose of 8 mg given intravenously over 2–5 min appears to be safe and is significantly more effective than placebo for the treatment of postoperative nausea and vomiting after intravenous anesthesia. Future studies comparing the antiemetic efficacy and side-effect profiles of various doses of ondansetron with those of other commonly used agents both for the treatment and prevention of postoperative nausea and vomiting are warranted.

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Antiemetic Efficacy of Ondansetron After Outpatient Laparoscopy

Matthew Bodner, MD, and Paul F. White, PhD, MD

Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri

The safety and efficacy of ondansetron were evaluated for the treatment of postoperative nausea and vomiting after laparoscopic surgical procedures. Seventy-one healthy, consenting outpatients were randomly assigned to one of two treatment groups according to a double-blind, placebo-controlled protocol. A standardized anesthetic technique consisting of alfentanil-thiopental-succinylcholine for induction and alfentanil-nitrous oxide-succinylcholine for maintenance of anesthesia was used. Patients in whom postoperative nausea and/or vomiting developed and persisted for ≥ 10 min received equivolemic intravenous injections of either ondansetron (8 mg) or saline (placebo) over a 2–5-min period. Ondansetron signif-

icantly decreased the posttreatment nausea scores (vs placebo) without increasing sedation or producing changes in cardiorespiratory parameters. In the placebo-treated group, 92% of the patients experienced subsequent episodes of vomiting in the postanesthesia care unit compared with 51% of the patients in the ondansetron group. Finally, only 43% of the ondansetron-treated patients required a "rescue" antiemetic compared with 86% in the placebo group. Thus, ondansetron (8 mg IV) was associated with a decreased incidence of nausea and vomiting after outpatient laparoscopic procedures.

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Nausea and vomiting are among the most unpleasant experiences associated with ambulatory surgery. In addition, the occurrence of intractable postoperative nausea and vomiting is the most frequent anesthetic-related cause for unexpected hospital admission of surgical outpatients (1,2). Most of the currently used antiemetic drugs (e.g., antihistaminics, anticholinergics, dopamine receptor antagonists) possess clinically significant side effects (e.g., sedation, α -adrenergic blockade, dry mouth, dysphoria, restlessness, and extrapyramidal symptoms).

Ondansetron is a carbazalone derivative that is structurally related to serotonin (Figure 1) and possesses specific 5-hydroxytryptamine (5-HT) subtype 3 receptor antagonism, without altering dopamine, histamine, or adrenergic or cholinergic receptor activity (3). Before initiating comparative clinical trials, it was necessary to determine if the maximum allowable dose of ondansetron possessed significant antiemetic activity in the postoperative setting. (At the time this investigation was performed, 8 mg of ondansetron was the maximal

dose we were permitted to use for the treatment of acute postoperative emetic symptoms. [Personal communication with Alan F. Joslyn, Ph.D., Glaxo, 5 Moore Drive, Research Triangle Park, NC 27709].) Therefore, we designed a randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy and safety of ondansetron when used to treat postoperative nausea and vomiting in outpatients undergoing elective laparoscopic surgical procedures.

Methods

One hundred fifty-five healthy nonpregnant female outpatients, aged 18–45 yr, scheduled to undergo diagnostic laparoscopy or laparoscopic tubal ligation procedures gave written informed consent to participate in the study should they develop nausea and vomiting after their operation. Institutional review board approval was obtained from the Washington University Human Studies Committee. A preoperative health screening questionnaire was completed by all the patients. Exclusionary criteria included patients who had taken an antiemetic or psychoactive medication within 24 hours before surgery, those who were more than 25% above ideal body weight, and those with a serum creatinine concentration greater than 2.0 mg/dL or an alanine aminotransferase concentration greater than 200 IU/L. A nega-

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Address correspondence to Dr. White, Department of Anesthesiology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8054, St. Louis, MO 63110.

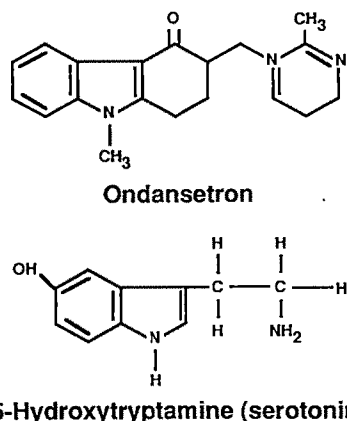


Figure 1. Chemical structures of 5-hydroxytryptamine (serotonin) and ondansetron (GR 38032F).

tive pregnancy test result was obtained for each patient before she entered the study.

All patients received the same anesthetic technique consisting of alfentanil (25–50 $\mu\text{g/kg}$ IV), thiopental (2–5 mg/kg IV), and succinylcholine (1–1.5 mg/kg IV) for induction and alfentanil (0.5–1.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ IV), succinylcholine (50–150 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ IV), and 70% nitrous oxide in oxygen for maintenance of anesthesia. Isoflurane (0.25%–0.5%) was administered if needed to maintain hemodynamic stability (i.e., arterial blood pressure and heart rate within 15% of their preinduction baseline values). Patients who complained of persistent nausea (lasting ≥ 10 min) and/or experienced at least two episodes of emesis or retching after entering the recovery room were given either ondansetron ($n = 35$) or saline ($n = 36$) according to a randomized, double-blind protocol. The randomization scheme was computer-generated by the sponsor.

Ondansetron (1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, hydrochloride dihydrate) in citrate buffer at pH 3.5 was supplied by the manufacturer (Glaxo, Inc., Research Triangle Park, N.C.) in 8-mg (2 mg/mL) aliquots that were diluted to 20 mL with normal saline by the hospital pharmacist. Identically labeled vials containing 4 mL of the citrate buffer at pH 3.5 were diluted to 20 mL with normal saline and administered as the placebo treatment. The study medication was infused intravenously over a 2–5-min interval to minimize pain on injection. Vital signs were recorded at 1–2-min intervals for the first 10 min and subsequently at 5-min intervals for 60 min after study drug administration. Patients who continued to vomit or experienced persistent nausea lasting ≥ 30 min after administration of the study drug were given “rescue” antiemetic medication consisting of 20 mg of metoclopramide and 25 mg of hydroxyzine diluted in 50 mL of normal saline and infused over 10–15 min. Patients

requiring additional antiemetic therapy because of persistent or recurrent nausea or vomiting after the rescue combination of metoclopramide and hydroxyzine were given 0.625–1.25 mg of droperidol intravenously.

The number of emetic episodes during the initial 4-h postoperative study period was recorded. Nausea was assessed using an 11-point verbal nausea scale (0 = no nausea to 10 = nausea “as bad as it could be”) just before treatment and then every 30 min until the patients were discharged from the Barnes Hospital Outpatient Surgery Center (i.e., when they satisfied standardized discharge criteria). Linear visual analogue scales (4) (0 = no nausea to 100 = severe nausea) were also used to assess nausea just before (0 min) and at 5-, 10-, 15-, 30-, 60-, 90-, and 120-min intervals after treatment. In addition, linear visual analogue scales were used to assess sedation, anxiety, and pain (0 = minimal to 100 = maximal effect) at the same time intervals. Monitoring in the postanesthesia care unit included arterial blood pressure, heart rate, respiratory rate, and oxygen saturation. These data were recorded before and 2, 4, 6, 8, 10, 20, 30, and 60 min after study drug (ondansetron or saline) administration. The research nurse noted the times to ambulation and discharge, as well as any postoperative complications. During the 24-h post-treatment period, patients recorded the number of emetic episodes, an overall nausea score (using the same 11-point scale), and the need for antiemetic and analgesic medications on a follow-up questionnaire (diary). In addition, all side effects experienced by the patient after discharge were recorded in this diary. Ninety-three percent of these questionnaires were returned to the investigators.

These data were analyzed with the Stata statistical program using analysis of variance (on continuous variables) and nonparametric methods (χ^2 , Kruskal-Wallis), with P values < 0.05 considered statistically significant. Bonferroni’s correction for multiple comparisons between treatment group means was also applied. The Wilcoxon rank sum test was used to determine differences in the median verbal nausea scores. The differences in nausea visual analogue scores before and after treatment were calculated for individual patients at each time point during the first 60 min after drug treatment. The overall mean paired differences for the two treatment groups were compared using repeated measures of analysis of variance. Values are reported as mean \pm SD (except as noted in the figures).

Results

Although the ondansetron (vs saline) group was younger (29 ± 6 vs 33 ± 6 yr, $P = 0.046$); there were no significant differences between the two treatment

Table 1. Demographic Data and Total Dosages of Anesthetic, Analgesic, and Muscle Relaxant Drugs for the Two Treatment Groups

	Saline	Ondansetron
Number (n)	36	35
Age (yr)	33 ± 6	29 ± 6 ^a
Weight (kg)	66 ± 13	66 ± 13
Height (cm)	164 ± 8	165 ± 9
No previous general anesthetic	4	10
History of postoperative nausea/vomiting	6	6
Duration of anesthesia (min)	79 ± 54	75 ± 44
Thiopental dose (mg)	303 ± 112	296 ± 102
Succinylcholine dose (mg)	121 ± 82	105 ± 68
Alfentanil dose (mg)	6.2 ± 3.3	6.2 ± 2.7
Isoflurane used to maintain hemodynamic stability %	12	8

Mean value ± SD (or numbers).

^aSignificantly different from the placebo group; $P = 0.046$.**Table 2.** Number of Episodes of Emesis in the Two Groups After Treatment With the Study Drug and Rescue Medication

	Saline	Ondansetron
Recurrence at 0-2 h		
None	3	17 ^a
1 Episode	2	2
2-4 Episodes	0	1
>4 Episodes ^b	31	15 ^a
Recurrence after rescue medication		
At 2-4 h	15	5 ^a
At 4-24 h	8	3

^aSignificantly different from the placebo group; $P < 0.01$.^bThese patients all received rescue antiemetic medication.

groups with respect to weight, height, types of surgical procedures, duration of anesthesia, or anesthetic drugs (Table 1). Analysis of patient responses to the preoperative screening questionnaire revealed no significant differences between the two groups with respect to medication allergies, alcohol or drug intake, or history of nausea/vomiting after previous operations.

The efficacy of ondansetron compared with placebo treatment is summarized in Tables 2 and 3 and Figures 2A and 2B. Of the ondansetron-treated patients, 49% experienced no subsequent emetic episodes during their stay in the postanesthesia care unit; however, 43% required subsequent rescue antiemetic medication for continued (or recurrent) retching or vomiting. Of the placebo-treated patients, only 8% experienced no subsequent emetic episodes and 86% required a rescue antiemetic. After treatment with the study drug, the ondansetron group had significantly lower nausea scores (Figure 2). The verbal nausea scores 30 and 60 min after treatment

Table 3. Number of Episodes and Timing of Vomiting and Antiemetic Rescue Therapy After Study Drug Administration

	Saline	Ondansetron
Median time to first episode of emesis after study drug (min)	33	102 ^a
Required rescue therapy	31	15 ^a
Required second antiemetic rescue	13	1 ^a
Vomiting after discharge	7	2
Antiemetic therapy after discharge	3	1

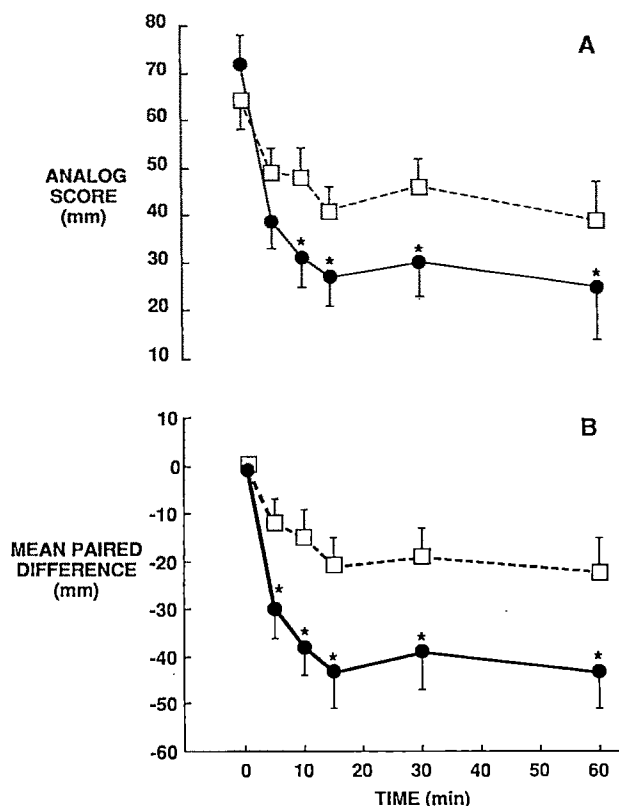
^aSignificantly different from placebo group; $P < 0.05$.

Figure 2. A. Nausea visual analogue scores (0 = none to 100 = severe) after saline (□) or ondansetron (●) administration. B. Mean paired differences in individual patient nausea scores after saline (□) or ondansetron (●). The zero point (0) refers to the values at the time the study drug was administered. Mean values ± SEM. * $P < 0.05$ considered statistically significant.

with the study drug were significantly lower in the ondansetron-treated patients (median score of 2 and 1, respectively) compared with those receiving the placebo (median scores of 5 and 4, respectively; $P < 0.01$). The administration of ondansetron was not associated with an acute change in the sedation score compared with saline (Figure 3). In contrast to the saline-treated patients (86% of whom received a rescue combination consisting of metoclopramide and hydroxyzine), the level of postoperative sedation was

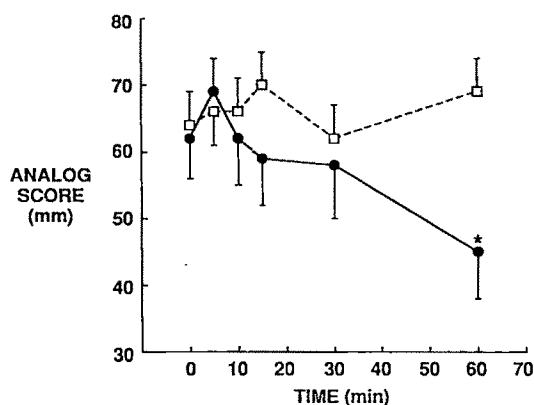


Figure 3. Sedation visual analogue scores (0 = completely awake to 100 = extremely sleepy) after saline (□) or ondansetron (●) administration. Mean values \pm SEM. * $P < 0.05$ considered statistically significant.

Table 4. Number of Adverse Events Reported in the Initial 24-h Period After Treatment With Study Medication

	Saline	Ondansetron
Headache	1	2
Dizziness	3	2
Flush sensation	0	1
Diplopia	1	0
Discomfort at IV site	4	4
Generalized pruritus	1	0
Urticaria	1	0
Swelling of face	1	0
Number of patients (No. of events)	9 (12)	9 (9)

decreased at the 60-min posttreatment testing interval in the ondansetron-treated patients. Interestingly, 42% of the control (saline-treated) patients who received the antiemetic rescue combination required further (second rescue) antiemetic therapy with droperidol (Table 3).

No significant differences were noted between the two groups with respect to heart rate, arterial blood pressure, respiratory rate, or oxygen saturation during the 60-min posttreatment period after study drug administration. Minor side effects were reported by 26% of the patients in the ondansetron group and 25% of the patients in the placebo group during the 24-h period after administration of the study medication and rescue antiemetic therapy (Table 4). Post-treatment pain and anxiety analogue scores were similar for the two study groups. There also were no significant differences between the ondansetron- and placebo-treated groups with respect to postoperative complications. Similarly, the time to discharge was identical in the placebo- and ondansetron-treated groups (188 ± 60 and 191 ± 63 min, respectively).

Discussion

The most commonly used antiemetic medications are antihistamines, anticholinergics, and dopamine receptor antagonists. Unfortunately, these drugs cause side effects such as hypotension, sedation, restlessness, dysphoria, and extrapyramidal symptoms (5,6). Ondansetron, a selective antagonist of 5-HT₃ receptors, is allegedly devoid of activity at dopaminergic, histaminergic, adrenergic, and cholinergic receptors. The 5-HT₃ receptor appears to mediate physiologic responses both in the peripheral nervous system (7) and in the vomiting (emesis) center of the central nervous system (8). Clinical studies have demonstrated that 5-HT₃ receptor antagonists decrease retching and vomiting in response to cytotoxic drugs (e.g., cisplatin) (9-12).

In 1987, Cunningham et al. (10) reported on the successful use of ondansetron for prophylaxis and treatment of the nausea and vomiting associated with cancer chemotherapy. When used for prevention and/or treatment of emesis associated with cancer chemotherapeutic agents, ondansetron is more effective than high-dose metoclopramide and without clinically significant side effects (12). The principal side effects attributed to ondansetron include occasional burning on injection and headache.

In the present study, ondansetron (8 mg IV) was significantly more effective than placebo in the treatment of postoperative nausea and vomiting in outpatients undergoing laparoscopic surgical procedures. Although the antiemetic dose we studied was only partially effective, this action was achieved without producing sedation or other clinically significant side effects. Higher doses of ondansetron are more effective in treating chemotherapy-induced emesis (11,12). In the future, dose-ranging studies will be necessary to determine the optimal dose of ondansetron for the treatment of postoperative nausea and vomiting.

Many factors can predispose outpatients to develop nausea and emesis after ambulatory surgery (13). In an effort to minimize the influence of the operation and anesthesia on our results, we used a female surgical population undergoing a standardized outpatient surgical procedure that would place them at high risk of developing postoperative nausea and vomiting. Not surprisingly, the opioid-based anesthetic technique was associated with a high incidence of nausea and vomiting (14). However, neither study group received prophylactic antiemetic drugs, and the dosages of opioid analgesic (alfentanil) were identical in the two treatment groups. A similar number of women in each treatment group had a history of nausea and vomiting after a previous general anesthetic. Although there was a small but

statistically significant difference in the mean ages of the two treatment groups, further data analysis revealed no age-related effect on our study results.

The lack of an "active" comparative drug certainly limits the clinical implications of this study. However, before initiating comparative trials with a new drug it was necessary to determine if the maximal allowable dose of ondansetron (8 mg IV) possessed significant antiemetic activity in the postoperative setting. Future studies will need to compare the optimally effective dose of ondansetron (determined from a proper dose-ranging study) with other standard antiemetic treatment regimens.

This clinical study can be further criticized because the use of rescue antiemetic therapy would have an effect on the subsequent visual analogue scores, side effects, and discharge times, and would complicate the interpretation of follow-up data. Nevertheless, data for both treatment groups were analyzed in an identical fashion. Although not directly comparable because of the study design, our data would suggest that ondansetron was as efficacious as the rescue combination consisting of metoclopramide (20 mg IV) and hydroxyzine (25 mg IV) in the previously untreated (placebo) group (Table 3). That is, 42% of the saline-treated group who received the rescue combination required a second rescue medication. Furthermore, the use of ondansetron was not associated with side effects that have been described with the administration of some commonly used antiemetic drugs (e.g., dysphoric reactions, restlessness, sedation). The failure to find a difference in recovery times was related in part to the postoperative testing procedures that were required to complete the study protocol. The necessity of completing these tests might explain why we failed to find a difference in the time to discharge even though the ondansetron-treated patients experienced fewer episodes of emesis 2-4 h after receiving the study medication.

In conclusion, ondansetron is an antiemetic drug that appears to be safe for treating acute postoperative nausea and vomiting. As ondansetron (8 mg IV) was only partially effective in treating postoperative emetic sequelae, further studies are needed to determine the optimal dose of ondansetron for both the treatment and prevention of emetic sequelae in the outpatient setting.

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Ibuprofen Provides Longer Lasting Analgesia Than Fentanyl After Laparoscopic Surgery

Martin Rosenblum, PhD, MD, Robert S. Weller, MD, Pattilyn L. Conard, CRNA, Ellen A. Falvey, RN, and Jeffrey B. Gross, MD

Department of Anesthesiology, University of Connecticut School of Medicine, Farmington, Connecticut

The authors compared the analgesic efficacy of one dose of oral ibuprofen with that of intravenously administered fentanyl for relief of pain after outpatient laparoscopic surgery. Thirty healthy female patients received either 800 mg of oral ibuprofen preoperatively or 75 μ g of intravenous fentanyl intraoperatively plus respective intravenous or oral placebos in a randomized, double-blind manner. Patients recorded their degree of pain and nausea in the recovery room, in the same-day surgery stepdown unit, during the ride home, and upon arrival at home. The postanesthesia care nurse recorded the

amount of fentanyl and droperidol needed to treat pain and nausea in the recovery room. Patients who received ibuprofen were more comfortable in the stepdown unit ($P < 0.05$) and after arrival home ($P < 0.05$) than those in the fentanyl group. Additionally, patients who received ibuprofen had lower nausea scores in the step-down unit ($P < 0.05$); this may have been related to the lower total fentanyl dose in these patients. The authors conclude that ibuprofen may be a useful alternative to fentanyl for providing postoperative analgesia for outpatient surgery.

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After laparoscopy for gynecologic surgery, patients often complain of abdominal discomfort, shoulder pain, and uterine cramps; these are commonly treated with opioid analgesics. Opioids, however, may increase the incidence of nausea and vomiting after laparoscopy, thus possibly prolonging recovery room stays (1). Although it is primarily an antiinflammatory agent, ibuprofen can provide effective analgesia for patients with mild-to-moderate postoperative pain (2-7). In addition, because ibuprofen decreases prostaglandin concentrations in menstrual fluid, it is the drug of choice for treating dysmenorrhea (8). Such prostaglandins may contribute to postlaparoscopy pain; therefore, ibuprofen may be especially suited to provide analgesia after gynecologic surgery. We designed the present randomized, double-blind study to compare the efficacy of ibuprofen with that of fentanyl for relieving pain after laparoscopic surgery.

Methods

Thirty consenting nonpregnant, ASA physical status I or II female patients scheduled for outpatient lapa-

roscopic surgery for infertility (lysis of adhesions and excision of endometriosis with a CO₂ laser) participated in this study approved by our institutional review board. We excluded patients with histories of allergy or adverse reactions to nonsteroidal antiinflammatory agents, peptic ulcer disease, and coagulation disorders, as well as those whose operation was scheduled to last longer than 2.5 h. We assigned patients to receive either 75 μ g of fentanyl or 800 mg of ibuprofen for postoperative analgesia based on a randomization table. Patients in the ibuprofen group received 800 mg of ibuprofen orally 1 h before the operation and 1.5 mL of a saline placebo intravenously 30 min before the anticipated end of the operation, whereas patients in the fentanyl group received an oral placebo 1 h before the operation and 75 μ g of fentanyl intravenously 30 min before the estimated time of completion of the operation. All study drugs and placebos were prepared by the hospital pharmacy; the patient, the anesthesia care team, and the investigators evaluating the patient were unaware of the study group assignment.

After induction of anesthesia and paralysis with 4 mg/kg of thiopental and 0.1 mg/kg of vecuronium, respectively, tracheal intubation was performed. We controlled ventilation and maintained anesthesia with isoflurane and 50% N₂O in O₂. The anesthesiologist, who was unaware of the study group assign-

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Address correspondence to Dr. Rosenblum, Department of Anesthesiology, University of Connecticut School of Medicine, Farmington, CT 06032.

Table 1. Discomfort Scores Used to Determine Need for Additional Fentanyl in the Postanesthesia Care Unit

Score	Condition
0	Quiet and comfortable
1	Sedate but uncomfortable
2	Restless and agitated
3	Uncontrollably agitated

ment, adjusted the isoflurane concentration based on routine clinical criteria. At the end of surgery, we aspirated each patient's gastric contents via an orogastric tube and reversed residual neuromuscular blockade with intravenous administration of 3 mg of neostigmine and 0.6 mg of glycopyrrolate. Patients breathed spontaneously until they awakened, at which time we removed the endotracheal tube and transferred them to the recovery room.

At 5, 15, 30, 60, and 90 min after the patients arrived in the recovery room, one of the investigators used the 4-point scale shown in Table 1 to determine whether additional analgesia was necessary. At the same times, we recorded the presence and severity of nausea and vomiting on a scale ranging from 0 (no nausea) to 3 (severe nausea with recurrent vomiting). At 15, 30, 60, and 90 min after arrival in the postanesthesia care area, patients evaluated their own pain on a 10-cm visual analogue pain scale.

Patients whose discomfort score in the postanesthesia care area was 2 or 3 (Table 1) received incremental doses of 25 μ g of fentanyl intravenously until they were comfortable (discomfort score < 2). Note that if fentanyl was necessary during the first half-hour postoperatively, we asked patients to score their pain on the visual analogue pain scale before receiving the first dose of fentanyl. In addition to the pain and nausea scores, we also recorded the duration of the postanesthesia recovery period and the total dose of fentanyl administered. We asked all patients to complete a postoperative questionnaire regarding their level of pain (10-point scale) and degree of nausea (4-point scale) at several times after discharge from the recovery room: in the same-day surgery stepdown unit, during the ride home, and after arrival at home. Patients were instructed to call us if pain, nausea, or vomiting were intractable.

We analyzed pain data using two-way analysis of variance (9), with Tukey *t*-tests for individual times if overall significance was present. We analyzed nausea data using Bonferroni-corrected Wilcoxon rank-sum tests. For demographic data, we used one-way analysis of variance. To determine if postoperative nausea was related to the total dose of fentanyl, we used Spearman rank correlation. Values are shown as mean \pm SE, with $P < 0.05$ indicating significance throughout the analysis.

Table 2. Comparison of the Ibuprofen and Fentanyl Groups

	Ibuprofen (<i>n</i> = 15)	Fentanyl (<i>n</i> = 15)
Age (yr)	29 \pm 1.2	30 \pm 1.0
Height (cm)	165 \pm 1.5	165 \pm 2.3
Weight (kg)	60.9 \pm 2.6	59.1 \pm 2.5
Duration of operation (min)	85 \pm 7.1	99.4 \pm 9.8
Time in the PACU (min)	99 \pm 4.0	104 \pm 4.0
Number of patients requiring fentanyl in the PACU	10	9
Fentanyl dose in the PACU (μ g)	36.7 \pm 9.1	26.7 \pm 6.7
Total fentanyl dose (μ g)	36.7 \pm 9.1 ^a	101.7 \pm 6.7
Number of patients requiring droperidol in the PACU	7	5
Postoperative droperidol (mg)	0.29 \pm 0.08	0.21 \pm 0.08

PACU, postanesthesia care unit.

Values are mean \pm SE.

^a $P < 0.05$ vs fentanyl.

Results

Age, height, weight, duration of surgery, time in the recovery room, and postoperative droperidol dose did not differ significantly between patients in the ibuprofen and fentanyl groups (Table 2). The investigator's assessment of discomfort in the recovery room did not differ between groups; this was confirmed by the fact that patients in each group received similar doses of fentanyl in the recovery room. However, as might be expected, patients in the fentanyl group received a larger total (intraoperative *plus* postoperative) dose of fentanyl than those in the ibuprofen group. Neither epigastric pain nor heartburn developed in any of the patients as a result of the ibuprofen therapy.

Analysis of variance revealed that patients who received ibuprofen had significantly less pain in the postoperative period than those in the fentanyl group (Figure 1, $P < 0.001$). Post hoc testing revealed that this overall difference could be attributed to differences observed in the stepdown unit and after patients arrived at home. Patients who received ibuprofen also reported significantly less nausea in the same-day surgery unit than those in the fentanyl group (Figure 2, $P < 0.05$). There was a significant correlation between severity of nausea in the same-day surgery unit and the total fentanyl dose (Figure 3, $r = 0.59$, $P < 0.01$).

Discussion

With the proliferation of same-day surgery, anesthesiologists must reevaluate strategies for postoperative pain management. In the outpatient setting, it is especially important to avoid side effects such as

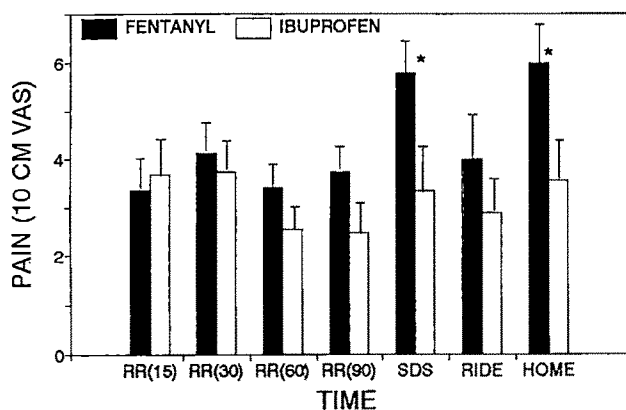


Figure 1. Pain as evaluated by patients (10-cm visual analogue scale) after laparoscopic surgery. Assessments were made 15, 30, 60, and 90 min after arrival in the recovery room (RR), as well as in the same-day surgery stepdown unit (SDS), during the ride home (RIDE), and after arrival home (HOME). * $P < 0.05$ vs ibuprofen group.

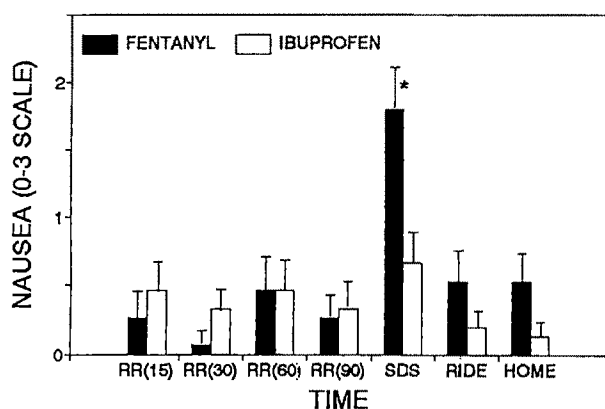


Figure 2. Assessment of nausea (0-3 scale, see text) after laparoscopic surgery. Assessments were made 15, 30, 60, and 90 min after arrival in the recovery room (RR), as well as in the same-day surgery stepdown unit (SDS), during the ride home (RIDE), and after arrival home (HOME). * $P < 0.05$ vs ibuprofen group.

excessive sedation, nausea, and vomiting, while providing effective analgesia. In fact, Gold et al. (10) found that pain, vomiting, and postoperative somnolence are the most common reasons for unanticipated hospital admission after same-day surgery.

In the present study, 800 mg of oral ibuprofen provided longer lasting analgesia than did 75 μ g of intravenous fentanyl after laparoscopic surgery. The validity of this conclusion is based on the premise that the patients received equal analgesic doses of the two therapies (i.e., ibuprofen and fentanyl). Unfortunately, there are no studies directly comparing the analgesic potency of ibuprofen with that of parenterally administered narcotics. However, the maximum analgesic effect that can be obtained from nonsteroidal antiinflammatory drugs appears to be equivalent to that of 8-10 mg of morphine administered intra-

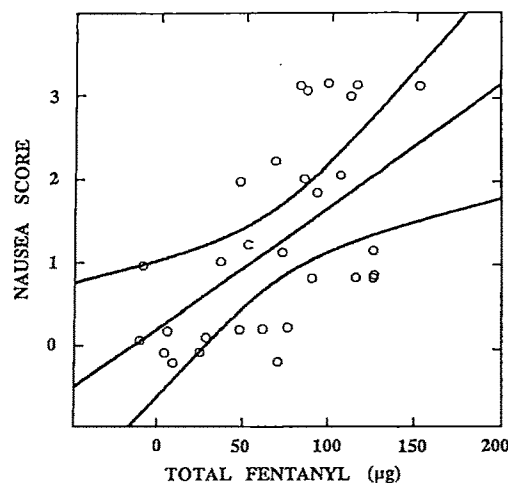


Figure 3. Severity of nausea (0-3 scale, see text) in the same-day surgery stepdown unit versus total perioperative fentanyl dose (μ g). The least-squares regression line ($r = 0.59$, $P < 0.01$) and its 95% confidence limits are shown.

muscularly (11-13). An 800-mg oral dose provides the maximum analgesia obtainable with ibuprofen (14); this dose should be approximately equianalgesic to 75 μ g of fentanyl assuming a 100:1 potency ratio of fentanyl to morphine (15). Furthermore, our finding that the patients required equal fentanyl doses in the postanesthesia care unit suggests that 75 μ g of fentanyl and 800 mg of ibuprofen were approximately equianalgesic under the conditions of this study.

Nonsteroidal antiinflammatory drugs act peripherally as well as centrally. Peripherally, their mechanism of action is to inhibit the cyclooxygenase enzyme system that metabolizes arachidonic acid to its endoperoxide intermediates (14). This results in decreased production of thromboxanes, prostacyclins, and prostaglandins. Thus, fewer intermediates and end products of the arachidonic acid cascade are available to interact with local mediators of inflammation such as bradykinin, histamine, and 5-hydroxytryptamine to promote erythema, edema, and pain, or to promote uterine contractions. Nonsteroidal antiinflammatory drugs may also act centrally to decrease pain by inhibiting cyclooxygenase within the central nervous system (14).

Ibuprofen may be particularly effective in treating perioperative pain after gynecologic procedures because of its peripheral effect on prostaglandin synthesis. By decreasing elevated prostaglandin levels, ibuprofen effectively relieves uterine pain associated with both primary dysmenorrhea (8,16-18) and secondary dysmenorrhea induced by intrauterine devices (8,18). A similar mechanism may help to relieve the pain that follows surgical manipulation of the uterus.

Our results confirm previous reports suggesting

that ibuprofen compares favorably with moderate doses of opioids for postoperative analgesia. For example, after dental surgery, 400 mg of ibuprofen is more effective than 30 mg of codeine (2), 30 mg of dihydrocodeine (3), 65 mg of propoxyphene (4), aspirin-codeine (650 mg/60 mg) (5), acetaminophen-codeine (600 mg/60 mg) (5), and aspirin-codeine-caffeine (375 mg/30 mg/30 mg) (6). After herniorrhaphy, the analgesic efficacy of 400 mg of oral ibuprofen is intermediate between that of aspirin-codeine-caffeine (375 mg/30 mg/30 mg) and that of aspirin-codeine-caffeine (750 mg/16 mg/60 mg) (7).

Our observation that the difference in pain control between ibuprofen and fentanyl first became apparent in the same-day surgery unit may be related to differences in the pharmacokinetics of the two analgesics. Although fentanyl has a long terminal elimination half-life (2.5–7 h), its duration of action after a small ($<7 \mu\text{g/kg}$) dose is primarily determined by redistribution (analogous to other lipid-soluble drugs such as thiopental) (19). After a single $1\text{-}\mu\text{g/kg}$ intravenous dose, such as patients received in the present study, plasma fentanyl levels can be expected to exceed the analgesic threshold for no longer than 2 h (20–22). In contrast, although the plasma elimination half-life of ibuprofen is 2 h (23), it is not fully absorbed from the gastrointestinal tract until 3 h after an 800-mg oral dose (23,24). Because of the complex interaction between absorption and elimination kinetics, the therapeutic effects of a single dose of ibuprofen may last more than 4 h (3–6,14). Because the mean duration of surgery in the present study was approximately 1.5 h, one would expect that by the time patients arrived in the same-day surgery unit, the analgesic effect of fentanyl was probably waning much more rapidly than that of ibuprofen.

Patients in the fentanyl group had a significantly more severe nausea and vomiting in the same-day surgery unit than those who received ibuprofen. In fact, the significant correlation between total fentanyl dose and nausea scores in the same-day surgery unit suggests that fentanyl was a causative factor. Opioids are well known to produce nausea and vomiting by direct stimulation of the chemoreceptor trigger zone (25). Nausea and vomiting are relatively uncommon in recumbent patients given opioids but increase significantly when patients move, suggesting that vestibular stimulation may potentiate the emetic effect (25). This is consistent with our observation that nausea was most severe when patients were transferred to the same-day surgery unit, where they first got out of bed.

Chronic ibuprofen therapy may cause gastrointestinal side effects (epigastric pain, nausea, heartburn, abdominal discomfort, and sensations of abdominal "fullness") in 5%–15% of patients (26). However, a

single perioperative dose of ibuprofen is almost always well tolerated (2–4,6). In the present study, we excluded patients who had prior histories of intolerance to nonsteroidal antiinflammatory drugs; therefore, our findings regarding postoperative nausea and vomiting do not apply to patients with such histories.

Of course, the present study compared fixed doses of ibuprofen and fentanyl. It is conceivable that had we chosen different doses of ibuprofen and/or fentanyl, or constructed dose-response curves for the two drugs, our results might have been different.

In summary, we observed that 800 mg of oral ibuprofen, given preoperatively to patients undergoing laparoscopic surgery of less than 2.5-h duration, provided longer lasting analgesia than $75 \mu\text{g}$ of intravenous fentanyl given intraoperatively. Furthermore, probably by decreasing the total perioperative dose of fentanyl, ibuprofen reduced postoperative nausea in the same-day surgery unit, where patients first ambulated and took oral fluids.

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Psychomotor Performance After Desflurane Anesthesia: A Comparison With Isoflurane

J. E. Fletcher, MB, BS, MRCP, FFARCS, P. S. Sebel, MB, BS, PhD, FFARCSI,
M. R. Murphy, MD, C. A. Smith, MD, S. A. Mick, RN, and M. P. Flister, CRNA

Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia

Recovery and psychomotor performance were studied in 80 ASA physical status I-III adult patients undergoing outpatient surgery. Patients were divided into four equal groups: thiopental induction of anesthesia followed by desflurane in nitrous oxide and oxygen (Th-DES-N₂O/O₂), thiopental induction of anesthesia followed by isoflurane in nitrous oxide and oxygen (Th-ISO-N₂O/O₂), thiopental induction of anesthesia followed by desflurane in oxygen (Th-DES-O₂), and desflurane inhaled induction followed by desflurane in oxygen (DES-DES-O₂). Patients were excluded from analysis if they required opioids or antiemetics postoperatively. The use of desflurane was associated with more rapid awakening compared with isoflurane (time to eye opening 9.45 ± 0.67 min [Th-DES-N₂O/O₂] and 13.8 ± 1.59 min [Th-ISO-N₂O/O₂], $P < 0.05$). Psychomotor performance was measured using the choice reaction time and critical

flicker fusion threshold. At 30 min after discontinuing anesthesia, five patients in the Th-ISO-N₂O/O₂ group and one patient in the Th-DES-N₂O/O₂ group were too sleepy to perform psychomotor tests. In addition, five patients who received Th-DES-O₂ and one patient who received the inhaled induction and maintenance of anesthesia with desflurane in oxygen were too sleepy to perform tests at 30 min. Patients receiving Th-DES-N₂O/O₂ showed less impairment of choice reaction time than those receiving Th-ISO-N₂O/O₂. Critical flicker fusion threshold, however, showed no difference between groups. The use of thiopental was associated with delayed recovery. Compared with isoflurane, desflurane anesthesia is associated with more rapid initial awakening and less impairment of choice reaction time.

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Animal studies have shown that desflurane results in more rapid recovery of motor coordination than does isoflurane or halothane (as measured by the rotarod test in rats) (1). The recovery times observed correlated with the blood/gas partition coefficients of the anesthetics used. Measurements of the inspired to end-tidal ratio of these anesthetics have also shown a more rapid equilibration with the less-soluble anesthetics, desflurane equilibrating most rapidly (2). Human studies have previously shown that in comparison with isoflurane, desflurane is associated with more rapid awakening at the end of surgery (3).

The purpose of this study was to investigate, in patients, whether initial awakening and recovery of psychomotor performance occurred more rapidly after desflurane or isoflurane anesthesia. We further

sought to determine the effects of thiopental and N₂O on performance after desflurane.

Methods

After obtaining approval from the human investigation committee, 80 consenting ASA physical status I-III patients (age, 40.7 ± 1.34 yr; weight, 77.0 ± 1.58 kg) scheduled for elective outpatient surgery were studied. Although patients classified as ASA physical status III could be included, those with clinically significant cardiovascular or pulmonary disease were excluded as these conditions might have affected anesthetic uptake and distribution.

Patients were randomly allocated to one of four equal groups: group 1, thiopental induction of anesthesia followed by desflurane in nitrous oxide and oxygen (Th-DES-N₂O/O₂); group 2, thiopental induction of anesthesia followed by isoflurane in nitrous oxide and oxygen (Th-ISO-N₂O/O₂); group 3, thiopental induction of anesthesia followed by desflurane in oxygen (Th-DES-O₂); group 4, desflurane inhaled induction followed by desflurane in oxygen.

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Address correspondence to Dr. Sebel, Department of Anesthesiology, Crawford Long Hospital of Emory University, Glenn Building, 25 Prescott Street NE, Atlanta, GA 30308.

Before induction of anesthesia, patients were moved to a screened area of the recovery room. Here the psychomotor test unit (critical flicker fusion threshold [CFFT] [4-6] and choice reaction time [CRT] [6,7]) was carefully explained to the patients, and time was allowed so the patients could practice and demonstrate to an observer that they understood their task. A baseline test of psychomotor performance was then made. The same recovery area was used for subsequent postoperative testing.

The choice reaction time was measured using a semicircular row of six light-emitting diodes (LEDs) mounted in a rectangular panel. Each LED had a button adjacent to it used to extinguish the light. At the base of the panel a centrally placed "ready" button was used to inform the computer that the patient was watching for a LED to light. Choice reaction time was measured as the time between the LED illuminating and the patient pressing the button next to the LED. Each of the six LEDs lit randomly 10 times in each test. The CFFT was performed by the patient watching four flickering LEDs recessed into a small shaded box. The patients held a button in readiness to indicate when they perceived that the flickering had ceased (i.e., the LEDs appeared to be on continuously). The LEDs began flickering at a frequency of 10 Hz, and the rate of flicker increased by 1 Hz every 2 s to a potential maximum flicker rate of 50 Hz. The CFFT was taken as the mean of six results on each occasion. All aspects of recovery room assessment were conducted by an observer unaware of the anesthetic technique used.

After baseline testing, a fast running intravenous infusion of crystalloid solution was commenced, and patients were transferred to the operating room. Routine monitors were attached (Dinamap blood pressure monitor, oximeter, electrocardiogram). While the patients were breathing oxygen, 3 mg/70 kg of crystalloid solution was administered. In groups 1-3, induction of anesthesia was with thiopental up to 5 mg/kg. In group 4, induction of anesthesia was commenced with administration of 3% desflurane in oxygen via face mask. The concentration was then increased slowly until loss of the lash reflex was noted (approximately 4.7% end-tidal) to ensure patient acceptability. After the lash reflex was lost, the concentration was increased more rapidly. All patients received succinylcholine to facilitate endotracheal intubation. Ventilation was controlled to maintain an end-tidal P_{CO_2} of 30-35 mm Hg. Gas analysis during anesthesia was accomplished using the PB-254 (Puritan-Bennett) multigas analyzer, which had been modified to include the measurement of desflurane. The gas analyzer was calibrated against a commercial reference source on each occasion after a 30-min "warm-up" period. The end-tidal anesthetic concen-

tration was adjusted, depending on the age of the patient, to between 6.0% and 7.25% desflurane or 1.1% and 1.3% isoflurane (in patients receiving 60% nitrous oxide, groups 1 and 2), or between 8.0% and 9.7% desflurane (in patients not receiving nitrous oxide, groups 3 and 4). Patients aged 18-30 yr received the higher concentration, and patients more than 30 yr old received the lower concentration. The anesthetic concentration was maintained constant until the end of surgery when all anesthetics were abruptly discontinued and 6 L/min of fresh oxygen was delivered into the circuit.

The time of discontinuation of anesthetic agents was noted as time zero for all subsequent measurements. The time taken for patients to open their eyes was noted and then every 15 s patients were asked to obey a command (squeeze fingers) and give their name, date of birth, and orientation as to place. After this initial wake-up assessment, patients were returned to the recovery area. Psychomotor testing was performed at 30, 60, 90, and 120 min after discontinuing the anesthetic agents. At these times, the observer also rated the patient on a four-point scale for sedation, obtained a visual analogue pain score from the patient, and inquired about any nausea or vomiting. Postoperative pain was managed by the use of nerve blocks and local infiltration of local anesthetics where possible, supplemented by oral ibuprofen. Further analgesia (fentanyl: 12.5-25 μ g intravenous increments) was given if required. Patients were invited to return the following day to perform a repeat measurement of their psychomotor tests (41 patients returned).

Patients unable to perform the psychomotor tests because of excessive sedation were assigned a performance value similar to the worst value obtained by a patient who was able to carry out the particular test. For the CRT, the worst mean result produced by a patient was 1.479 s; and patients unable to perform the test were therefore assigned a score of 1.5 s. For the CFFT, the worst mean result produced by a patient was 17.8 Hz; and patients unable to perform the test were assigned a score of 17 Hz. This prevented the total elimination of this very important subgroup of patients from the data analysis but may have underestimated their degree of impairment.

Data are mean \pm se. As there were statistically significant differences between groups for CFFT at baseline, all statistical analyses of the psychomotor data were with repeated measures analysis of variance over the 30-120-min postoperative period using the baseline as covariate. Bonferroni *t*-tests were used for between-group comparison of the change from baseline. Other data were analyzed with *t*-test, χ^2 -test, or Mann-Whitney test as appropriate. Statistical significance was taken as $P < 0.05$.

Table 1. Population Characteristics

	Group			
	1 Th-DES-N ₂ O/O ₂	2 Th-ISO-N ₂ O/O ₂	3 Th-DES-O ₂	4 DES-DES-O ₂
Age (yr)	39.4 ± 2.7	40.2 ± 2.72	41.7 ± 3.0	41.7 ± 2.4
Weight (kg)	78.1 ± 3.9	80.3 ± 2.8	76.3 ± 2.7	73.3 ± 3.0
Height (cm)	174 ± 3.2	169 ± 6.0	169 ± 2.1	170 ± 11
Dose of thiopental (mg)	369 ± 24	342 ± 15	330 ± 14	—
Duration of anesthesia (min)	50.4 ± 4.1	45.8 ± 5.1	50.3 ± 6.3	53.6 ± 6.2
End-tidal anesthetic concentration at discontinuation (%)	6.1 ± 0.34	1.1 ± 0.04	8.9 ± 0.35	8.3 ± 0.41

Th, thiopental; DES, desflurane.
Data are mean ± SE.

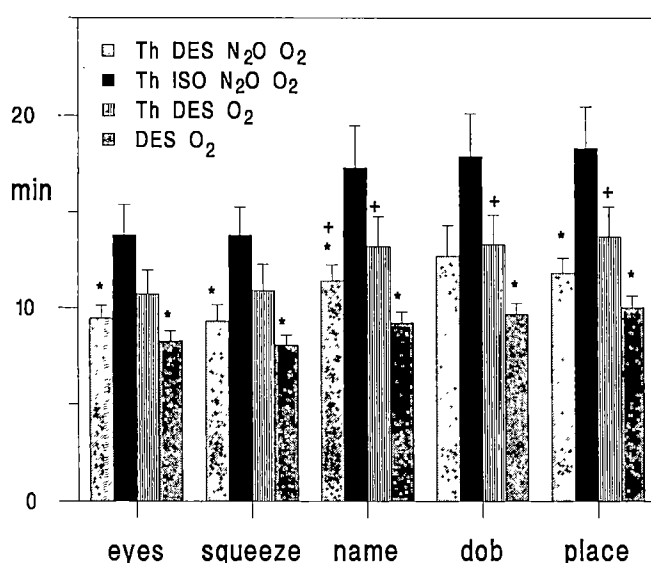


Figure 1. Early recovery times. Data are mean ± SE. Vertical axis shows time in minutes to open eyes (*eyes*), obey command "squeeze my hand" (*squeeze*), give name (*name*), give date of birth (*dob*), and answer question "where are you?" (*place*). * $P < 0.05$ compared with group 2 (thiopental-isoflurane-N₂O/O₂). + $P < 0.05$ compared with group 4 (desflurane inhaled induction of anesthesia-desflurane-O₂). (Student's *t*-test).

Results

There were no differences between groups for mean age, weight, height, thiopental induction of anesthesia dose, or duration of anesthesia (Table 1).

Analysis of the early wake-up times (Figure 1) showed that desflurane was associated with more rapid eye opening, response to command, and giving name and place than isoflurane (Th-DES-N₂O/O₂ vs Th-ISO-N₂O/O₂). A further comparison within the three desflurane groups showed that the addition of thiopental resulted in delay in patients giving their name, date of birth, and place (Th-DES-O₂ vs DES inhaled induction of anesthesia-DES-O₂) but that the inclusion of nitrous oxide did not affect the speed of waking (Th-DES-N₂O/O₂ vs Th-DES-O₂).

Several patients were so sleepy at 30 min that they were unable to cooperate with testing. Of the 12 such patients, five were in group 2 (Th-ISO-N₂O/O₂), five in group 3 (Th-DES-O₂) and one was in each of groups 1 and 4 (Th-DES-N₂O/O₂ and DES inhaled induction of anesthesia-DES-O₂, respectively). These differences did not achieve statistical significance (χ^2 -test, $P < 0.099$).

Psychomotor recovery and sedation data are presented for patients who did not receive fentanyl in the postoperative period, as it was found that administering fentanyl resulted in an increase in sedation and impairment of performance that confounded the data. Worsened sedation score was associated with fentanyl administration maximally at 60 min (χ^2 -test, $P < 0.005$). Fifty-five of 80 patients were therefore used for analysis. The distribution of these patients and the surgery they underwent are shown in Table 2.

Analysis of the sedation scores (Table 3) showed that there were differences between groups at 30 and 60 min. In particular, the effect of a thiopental induction of anesthesia was observed at 60 min (Th-DES-O₂ vs DES inhaled induction of anesthesia-DES-O₂). Differences also existed between the patients in group 2 (Th-ISO-N₂O/O₂) and group 4 (DES inhaled induction of anesthesia-DES-O₂) at 30 and 60 min and group 2 and group 3 (Th-DES-O₂) at 30 min.

Choice reaction time (Figure 2) showed differences between groups ($F = 3.10$, $P < 0.04$) and with time ($F = 32.2$, $P < 0.01$). Between-group comparisons of CRT showed that differences existed at 30 min between desflurane and isoflurane (group 1 [Th-DES-N₂O/O₂] vs group 2 [Th-ISO-N₂O/O₂]). In addition, a difference existed between the patients receiving a thiopental induction and those receiving the inhaled induction of anesthesia (group 3 [Th-DES-O₂] vs group 4). A further difference also existed between patients in the isoflurane group and those receiving the inhaled induction of anesthesia at both 30 and 60 min (groups 2 and 4).

Table 2. Type of Surgery in Patients Not Receiving Postoperative Fentanyl (i.e., those included in psychomotor analysis)

Operation	Group			
	1 Th-DES-N ₂ O/O ₂	2 Th-ISO-N ₂ O/O ₂	3 Th-DES-O ₂	4 DES-DES-O ₂
Arthroscopy	0	2	2	1
Hernia repair	3	2	3	3
Laparoscopy	0	1	1	1
Breast biopsy	1	0	2	2
Other biopsy	1	0	0	1
Scar revision	3	1	0	1
Circumcision	0	0	1	1
Septoplasty	0	2	0	1
D&C	1	1	3	4
Cystoscopy	1	4	3	1
Hemorrhoidectomy	0	1	0	0
Total	10	14	15	16

D&C, dilatation and curettage; Th, thiopental; DES, desflurane.

Table 3. Sedation Scores of Patients Not Receiving Fentanyl at Each Time Point Postoperatively

Group	Time (min)			
	30	60	90	120
Thiopental-desflurane-N ₂ O/O ₂	3.3 ± 0.21	3.7 ± 0.15	3.7 ± 0.15	4.0 ± 0.00
Thiopental-isoflurane-N ₂ O/O ₂	2.6 ± 0.27 ^{a,b}	3.4 ± 0.22 ^b	3.6 ± 0.17	3.8 ± 0.16
Thiopental-desflurane-O ₂	3.4 ± 0.21	3.5 ± 0.17 ^b	3.9 ± 0.09	3.9 ± 0.09
Desflurane inhaled induction-desflurane-O ₂	3.7 ± 0.13	3.9 ± 0.07	3.9 ± 0.07	3.9 ± 0.07

4 = awake, 3 = asleep but easily aroused, 2 = asleep and difficult to arouse, 1 = asleep and not arousable.

Data are mean ± SE.

^aP < 0.05 compared with desflurane inhaled induction-desflurane-O₂.^bP < 0.05 compared with thiopental induction-desflurane-O₂. (Mann-Whitney test.)

In contrast to CRT, CFFT (Figure 3) showed no differences between groups ($F = 2.18$, $P < 0.11$), although an effect of time was present ($F = 26.7$, $P < 0.01$).

At 24 h, comparison of the 41 patients able to return for psychomotor testing showed a general, although nonsignificant, improvement over baseline.

There was no difference at any time point between the visual analogue pain scores of the different groups, irrespective of whether fentanyl was needed or not. The visual analogue pain scores tended to decrease with time.

Vomiting occurred in 5% of patients in the 2 h after surgery. A further 14% of patients experienced nausea in the same time period with no difference between groups. Although there was a threefold increase in the tendency to be nauseated or vomit in the patients who received postoperative fentanyl, this did not achieve statistical significance (χ^2 -test, $P < 0.09$).

Discussion

Early recovery from the effects of anesthesia are particularly important in ambulatory patients where an early recovery to "street fitness" is desirable. In a review of methods of assessing early recovery from anesthesia, Hindmarch and Bhatti (8) concluded that both the CRT and CFFT were the most effective, and carefully studied, methods of distinguishing differences of recovery in the early postoperative period. These techniques have previously been successful in showing differences between propofol and thiopental anesthesia (7,9). We therefore elected to include these methods of assessment in our study.

Allocation of a psychomotor test value to the patients who were too sleepy to cooperate with testing at 30 min may underestimate their degree of impairment, as the value used was similar to the worst value obtained from a patient who was able to perform the tests. If this is the case, our arbitrary allocation will tend to eliminate differences between

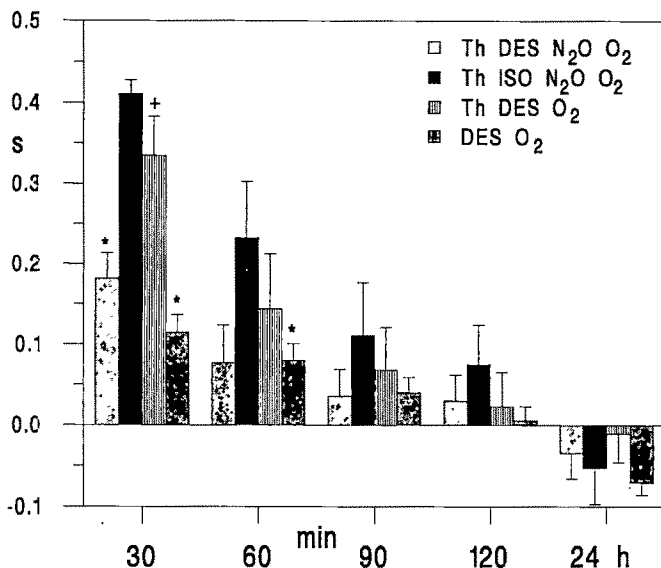


Figure 2. Choice reaction time. Data are mean \pm SE. Change from baseline of reaction time in the 2 h, and at 24 h, after discontinuing the anesthetics in four anesthetic techniques. Vertical axis shows change from baseline (s). Horizontal axis shows the four treatment groups at each time point. * $P < 0.05$ compared with group 2 (thiopental-isoflurane-N₂O/O₂). † $P < 0.05$ compared with group 4 (desflurane inhaled induction of anesthesia-desflurane-O₂). (Bonferroni *t*-test.)

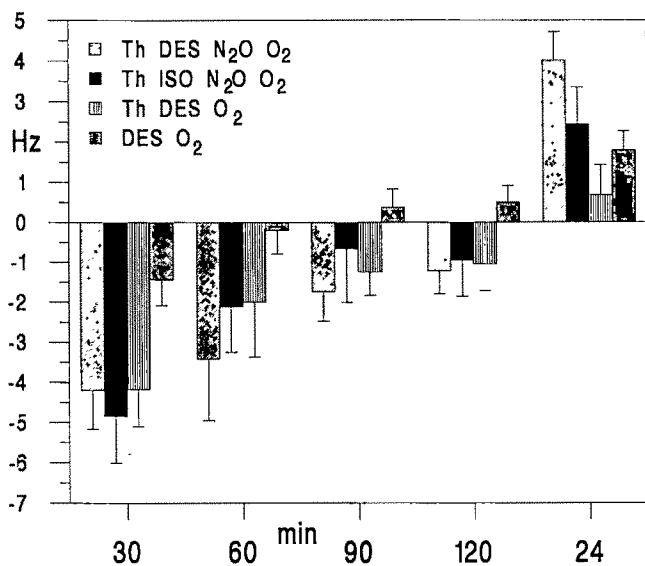


Figure 3. Critical flicker fusion threshold. Data are mean \pm SE. Change from baseline of critical flicker fusion threshold in the 2 h, and at 24 h, after discontinuing the anesthetic agents in four anesthetic techniques. Vertical axis shows change from baseline (Hz). Horizontal axis shows the four treatment groups at each time point.

groups, particularly in the most affected groups (group 2 [Th-ISO-N₂O/O₂] and group 3 [Th-DES-O₂]).

Based on the awakening times, the substitution of desflurane for isoflurane results in a more rapid initial

recovery. This finding confirms our previous comparison of recovery times with these two anesthetics. The difference observed in the CRT at 30 min further supports the suggestion that desflurane results in a more rapid recovery than does isoflurane. We were surprised to find that there were no differences in the CFFT. The reason for this is not clear. We chose to use the CFFT measured using ascending frequency only. This direction has previously been shown to be the most sensitive in detecting sedation in patients under rising nitrous oxide concentrations (6). However, measurement of only ascending frequency of flicker may have the disadvantage of allowing sleepy patients to delay recording that they have perceived fusion of the flickering light, when compared with more alert patients. This would tend to cancel the effect of perceiving fusion at a lower frequency and may be an explanation of the unexpected lack of differentiation of groups that we observed with this test. Critical flicker fusion threshold is a measure of ability to distinguish discrete sensory information and is an index of cortical activity (5,10). Critical flicker fusion threshold is the most sensitive test for diazepam sedation and to follow changes in attention, vigilance, decision making, learning, and memory (4). Thus, perhaps there is a genuine differential effect of the two anesthetic agents on different processing abilities in the brain. Previous studies using both these tests have shown similar results (7,9) when applied to recovery from general anesthesia, but have shown divergence between the two tasks during nitrous oxide sedation (6).

Our study shows little differences in performance between group 1 (Th-DES-N₂O/O₂) and group 3 (Th-DES-O₂). However, it should be noted that the MAC equivalents between these two groups were not equal. Group 1 received both 1 MAC desflurane and nitrous oxide. Assuming the MAC of nitrous oxide to be 1.05 ATM, this gives us an additive MAC of 1.57. The desflurane/oxygen group received only 1.33 MAC. Because at the time of initiating this study the cardiovascular effects of desflurane in higher doses were not well defined, we believed it inappropriate to use desflurane concentrations of greater than 1.33 MAC in this study.

We eliminated psychomotor performance data from all patients receiving fentanyl in the postoperative period. Small doses of fentanyl will produce a rapid and marked decrease in psychomotor performance for periods of up to 30 min. As we believed that fentanyl administration was related more to pain from the site of surgery and individual patient variability than to anesthetic conditions, we believed it appropriate to eliminate these patients. Thus, the psychomotor performance data reported in this study

are related entirely to the different anesthetic conditions and no opioids were used at all.

The effect of thiopental is clearly seen by comparing groups 3 (Th-DES-O₂) and 4 (DES inhaled induction of anesthesia-DES-O₂). Patients induced with thiopental took longer to state their name, date of birth, and place and showed more impairment of CRT at 30 min than those who received an inhaled induction of anesthesia. Previous studies of the effect on recovery of drugs intravenously administered to induce anesthesia have shown that thiopental is associated with the most marked and prolonged impairment when compared with methohexital (7) or propofol (7,11,12). In the report by Grant and Mackenzie (7), thiopental was associated with impaired performance compared with a group of control patients (of CFFT and total reaction time) for 90 min.

A clinically and economically important end point for a study of outpatient anesthesia is the time to discharge. This study design precluded any such assessment. Our patients were held in the postanesthesia care unit for 2 h after surgery to perform these psychomotor tests.

The findings of this study may not be equivalent to data obtained in normal clinical practice. Normal clinical practice will involve the gradual reduction of the volatile anesthetic concentration toward the end of the case. This will obviously result in a decreased recovery time. The mean time to open eyes in our group 2 patients (Th-ISO-N₂O/O₂) was 14 min. By reducing the isoflurane concentration toward the end of the case, it will obviously be possible to obtain faster recovery. It will not be possible to reduce desflurane concentrations in quite the same way as with isoflurane because of the probability of the patient becoming light toward the end of the anesthetic.

In conclusion, we have shown that when comparing desflurane with isoflurane, the use of desflurane is associated with a more rapid speed of initial waking and, subsequently, less impairment of CRT. Critical flicker fusion threshold, however, failed to distinguish between the two anesthetics. This study also

demonstrated that the use of thiopental delays recovery from desflurane anesthesia.

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Emergence Airway Complications in Children: A Comparison of Tracheal Extubation in Awake and Deeply Anesthetized Patients

Ramesh I. Patel, MD, Raafat S. Hannallah, MD, Janet Norden, MSN, William F. Casey, MB, and Susan T. Verghese, MD

Departments of Anesthesiology and Pediatrics, Children's National Medical Center and George Washington University School of Medicine and Health Sciences, Washington, D.C.

We compared the differences in oxygen saturation and airway-related complications after tracheal extubation in pediatric patients undergoing elective strabismus surgery or adenoidectomy and/or tonsillectomy who were awake versus anesthetized. Seventy otherwise healthy patients between 2 and 8 yr of age were studied. Anesthesia was induced with halothane or thiamylal and maintained with nitrous oxide and halothane. After induction of anesthesia, the patients were randomly assigned to group 1 (awake extubation) or group 2 (anesthetized extubation). Oxygen saturation was measured continuously and recorded 10 min before extubation and at 1, 2, 3, 5, 7, 10, 15, 20, 25, and 30 min after tracheal extubation. Supplemental oxygen was administered when oxy-

gen saturation values were less than 90% while breathing room air. Oxygen saturation levels were higher in group 2 than in group 1 at 1, 2, 3, and 5 min after extubation. There were no differences between the two groups in the number of patients requiring supplemental oxygen. The incidence of airway-related complications such as laryngospasm, croup, sore throat, excessive coughing, and arrhythmias was not different between the two groups. We conclude that the anesthesiologist's preference or surgical requirements may dictate the choice of extubation technique in otherwise healthy children undergoing elective surgery.

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Tracheal extubation can be performed while patients are deeply anesthetized or when they are awake. Awake extubation entails removing the endotracheal tube when the patient is awake and breathing adequately. Wakefulness is determined by a return of laryngeal and pharyngeal reflexes, eye opening, grimacing, coughing, and purposeful movements. Tracheal extubation during deep anesthesia is defined as removing the endotracheal tube during the surgical stage of general anesthesia while the patient is breathing spontaneously but the airway reflexes are still depressed.

Each technique has its own advantages and disadvantages. Coughing and straining associated with

awake extubation may lead to an increased incidence of sore throat and croup (1). Valsalva maneuver and breath-holding associated with coughing and bucking may cause a decrease in oxygen saturation (SpO_2) (2). One advantage of tracheal extubation during deep anesthesia is that patients are less likely to strain and cough during extubation.

This study compares the differences in SpO_2 and the incidence of airway-related complications such as laryngospasm, excessive coughing, sore throat, croup, and arrhythmias after awake and anesthetized extubation of the trachea in children undergoing strabismus surgery or tonsillectomy and/or adenoidectomy.

Methods

The study was approved by the institutional review committee, and written informed consent was obtained from parents. Seventy healthy (ASA physical status I or II) children between 2 and 8 yr of age were studied. Patients with a history of upper respiratory infection or asthma were not included. Premedication

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Address correspondence to Dr. Patel, Department of Anesthesiology, Children's National Medical Center, 111 Michigan Avenue, N.W., Washington, DC 20010.

was not given. All patients were required to fast appropriately according to our institutional guidelines. Anesthesia was induced by nitrous oxide, oxygen, and halothane administered through a mask or by 5–6 mg/kg of intravenous thiamylal. The technique of anesthesia induction was selected in collaboration with the patient and parents.

After induction of anesthesia, 0.01–0.02 mg/kg of atropine sulfate was administered intravenously. Tracheal intubation was performed with or without the use of succinylcholine. An air leak around the tracheal tube at a maximum pressure of 20 cm H₂O was confirmed by auscultation near the suprasternal area. If no leak was detected, the tube was replaced by a tracheal tube with an internal diameter 0.5 mm smaller than that of the previous tube, and the smaller tube was checked for the presence of an air leak. No other muscle relaxants were used intraoperatively. The patients were monitored with precordial stethoscope, electrocardiogram, blood pressure cuff (Dinamap, Critikon, Inc., Tampa, Fla.), temperature probe, pulse oximeter, and mass spectrometer (SARA, Allied Healthcare Products, Inc., St. Louis, Mo.). Anesthesia was maintained with nitrous oxide, oxygen, and halothane with assisted respirations. After induction of anesthesia, patients were randomly assigned to one of the two groups by opening a sequentially numbered sealed envelope. Patients assigned to group 1 underwent awake extubation, and those in group 2 underwent extubation during deep anesthesia.

After completion of the operation, group 1 patients received 100% oxygen for at least 5 min. Their tracheal tubes were removed when they demonstrated facial grimace, had adequate tidal volume and respiratory rate, coughed with open mouths or opened their eyes, and when the end-tidal halothane level was less than 0.15%. In group 2 patients, the tracheas were extubated during the surgical stage of general anesthesia when the end-tidal halothane level was greater than 0.8%. After extubation, 100% oxygen was administered through face mask for 5 min.

Patients were transported in the lateral position to the postanesthesia care unit (PACU) after assuring that they were able to maintain adequate air exchange. Oxygen saturation was measured continuously by a Nellcor pulse oximeter (Nellcor, Inc., Hayward, Calif.) in both groups while patients were breathing room air. The measurements continued until the patients were discharged from the PACU. Oxygen saturation was recorded when the patients were calm, and when their pulse oximeters showed consistent detection. Lowest measured SpO₂ values were recorded 10 min before tracheal extubation and at 1, 2, 3, 5, 7, 10, 15, 20, 25, and 30 min after tracheal extubation. Arterial desaturation (defined as SpO₂ of

Table 1. Oxygen Saturation Values in Awake Versus Deeply Anesthetized Patients Undergoing Tracheal Extubation

Values	Type of extubation	
	Awake (n = 36)	Deep (n = 34)
Age (mo)	48.5 ± 17.1	55.8 ± 19.7
Weight (kg)	17.0 ± 4.7	18.4 ± 3.8
SpO ₂		
Before extubation	98.6 ± 2.5	98.7 ± 1.7
1 min ^a	97.4 ± 5.7	99.8 ± 0.5
2 min ^b	96.1 ± 3.7	99.4 ± 0.9
3 min ^b	93.7 ± 4.8	98.7 ± 2.3
5 min ^b	94.3 ± 3.3	97.6 ± 3.7
7 min	94.1 ± 3.9	94.0 ± 5.9
10 min	94.7 ± 3.0	94.2 ± 4.7
15 min	95.1 ± 4.1	94.1 ± 3.9
20 min	96.1 ± 2.4	95.1 ± 4.0
25 min	96.3 ± 2.7	94.5 ± 5.1
30 min	96.8 ± 2.8	96.7 ± 2.1

SpO₂, oxygen saturation.

^aP < 0.02.

^bP < 0.0005, Student's *t*-test.

less than 90% for more than 30 s) was treated with supplemental oxygen administered through a face mask at a rate of 6 L/min. Supplemental oxygen was discontinued every 5 min, and its need was reassessed. Airway-related complications in the operating room such as laryngospasm, upper airway obstruction, and frequent or prolonged coughing episodes were noted. The electrocardiogram monitor was closely observed to detect arrhythmias. In the postanesthetic period, the patients were evaluated for signs and symptoms of croup after extubation by a blinded observer using Downes' Croup Score (3).

All patients or their parents were interviewed by telephone the following day regarding the presence or absence of a sore throat. Differences in the overall time-course of SpO₂ were analyzed using Hotelling's T²-test followed by Student's *t*-test at single instances of time. A statistical significance of *P* < 0.05 was considered acceptable. Complications after extubation were analyzed using either a χ^2 or Fisher's exact test.

Results

There were 36 patients in group 1 and 34 patients in group 2. Of the 36 patients in group 1, 18 underwent strabismus surgery and the remaining 18 underwent tonsillectomy and/or adenoidectomy (T/A). In group 2, 14 underwent strabismus surgery and 20 had T/A. The age and weight of patients in both groups were comparable (Table 1). Similarly, there was no difference in age and weight of patients in the different subgroups (e.g., T/A deep vs. T/A awake). Anesthe-

Table 2. Number of Patients With Airway-Related Complications in the Operating Room: Awake Versus Deeply Anesthetized Patients Undergoing Tracheal Extubation

Complication	Awake (n = 36)		Deep (n = 34)	
	Strabismus	T/A	Strabismus	T/A
Laryngospasm	0	0	0	2
Excessive coughing	1	1	0	4
Breath-holding	0	0	1	0
Airway obstruction requiring positive pressure ventilation	0	0	1	0
Arrhythmias	1	1	0	0
Total ^a	2	2	2	6

^a $P > 0.35$, Fisher's exact test.

sia was induced through a mask in 59 patients; 11 patients received intravenous thiamylal. Oxygen saturation was 100% before tracheal extubation in all patients, irrespective of the group assignment. As shown in Table 1, SpO_2 values were lower at 1, 2, 3, and 5 min after extubation in group 1 than in group 2 patients (Hotelling's T^2 , $P < 0.001$). Oxygen saturation values were similar thereafter. Twelve patients in group 1 and 14 in group 2 required supplemental oxygen. Of the 32 patients who underwent strabismus surgery, 4 of 18 in group 1 and 5 of 14 in group 2 required supplemental oxygen. Of the 38 patients who underwent T/A, 8 of 18 in group 1 and 9 of 20 in group 2 required supplemental oxygen. The difference between the number of group 1 and 2 patients requiring supplemental oxygen was not statistically significant.

There was no statistical difference ($P > 0.35$) between groups 1 and 2 with respect to the incidence of laryngospasm, excessive coughing, breath-holding, airway obstruction requiring positive pressure ventilation after extubation, or arrhythmias in the operating room (Table 2). Multiple premature ventricular contractions developed in two patients in group 2 before onset of spontaneous ventilation. The end-tidal CO_2 values in these patients were 53 and 55 mm Hg, and end-tidal halothane concentrations were 1.1 and 1.22, respectively. When a lighter level of anesthesia was tried to simulate spontaneous ventilation, it resulted in coughing. Therefore, the tracheas of both patients were extubated when they were awake.

The incidence of laryngospasm, croup, and sore throat during the recovery period was not different between the two groups. There was no difference in the incidence of sore throat between patients whose tracheas were intubated after succinylcholine administration and those who did not receive muscle relaxants before intubation. Similarly, there were no differences between the two groups in the incidence of

Table 3. Number of Patients With Postoperative Complications: Awake Versus Deeply Anesthetized Patients Undergoing Tracheal Extubation

Time/type of complication	Awake		Deep	
	Strabismus	T/A	Strabismus	T/A
Recovery period (hospital)				
Laryngospasm	0	0	0	1
Croup				
Hoarse voice	3	2	2	1
Barky cough	1	0	2	6
Stridor	0	0	0	0
Cyanosis	0	0	0	0
Sore throat				
No difficulty swallowing	0	9	0	6
Difficulty swallowing	0	4	0	2
Unable to swallow	0	0	0	0
At home				
Croup				
Hoarse voice	2	1	0	3
Barky cough	0	0	0	2
Stridor	0	0	0	0
Cyanosis	0	0	0	0
Sore throat				
No difficulty swallowing	0	10	1	12
Difficulty swallowing	0	4	1	1
Unable to swallow	0	0	0	0

T/A = tonsillectomy and/or adenoidectomy.

croup and sore throat after the patients' discharge from the hospital (Table 3).

Discussion

The tracheas of healthy children undergoing elective surgery can be extubated either when they are awake or during deep anesthesia. Before determining the technique of extubation, factors such as the patient's physical condition, skill of the anesthesiologist, and expertise of the recovery room staff must be considered. Patients with a full stomach or with a difficult airway, for example, should have their tracheas extubated only after they have regained full control of their airway reflexes and can maintain adequate ventilation (awake). However, in select patients such as those with asthma, it may be preferable to extubate the trachea while the patients are still anesthetized so that bucking and coughing can be avoided.

There are many different methods of performing extubation during deep anesthesia. Our approach is to maintain 50% nitrous oxide, halothane, and oxygen so that anesthetic depth remains constant. An alternate method is to discontinue nitrous oxide and increase the concentration of inhaled anesthetic. Although there are no studies comparing the two techniques, the outcome is likely to be influenced more by the skill and experience of the anesthesiolo-

gist than by the method alone. Lidocaine and opioids are sometimes administered before extubation during deep anesthesia to decrease the incidence of coughing and laryngospasm. However, Leicht et al. (4) concluded that 1.5 mg/kg of lidocaine does not prevent laryngospasm when extubation is carried out at the start of swallowing activity.

Croup and sore throat are also common postoperative complications that may be influenced by extubation technique. Koka et al. (1) noticed an increased incidence of croup after extubation in patients who coughed or strained while the endotracheal tube was in place. By contrast, we did not find any difference in the incidence of postoperative croup or sore throat between the two groups. This difference in observations could be attributed to the fact that an air leak was detected around the tracheal tubes at pressures below 20 cm H₂O in all our patients.

Hemoglobin desaturation after tracheal extubation is another concern. Previous studies indicate that arterial oxygen desaturation will develop in 21%–35% of healthy patients during transport from the operating room to the recovery room (2,5,6). Motoyama and Glazener (7) observed that 43% of the pediatric patients breathing room air in the recovery room had low SpO₂ values (<91%) in the early postanesthetic period. In patients who awoke promptly, SpO₂ increased rapidly from the initial arterial hemoglobin desaturation, whereas hemoglobin desaturation was protracted in those who remained asleep. We did not notice any difference in the incidence or timing of hemoglobin desaturation between the deeply anesthetized and awake extubation groups. This may be due to differences in patient selection, surgical procedures, and anesthetic technique. For example, whereas none of the patients in our study received narcotics, 36% of the patients in Motoyama and Glazener's study received narcotics as a premedicant or supplement.

Although we expected group 1 patients to exhibit oxygen desaturation before extubation because of bucking, coughing, and breath-holding that occurs during awake extubation, SpO₂ was 100% in all patients before extubation. Group 2 patients, on the other hand, were expected to have lower SpO₂ after extubation when they passed through the second stage of anesthesia. Our results indicate that SpO₂ values of patients whose tracheas were extubated when they were awake were similar to those of patients who underwent extubation during deep anesthesia at all times except the 5 min immediately after extubation when values in group 2 were higher than those in group 1. The initial difference in SpO₂ may be of limited clinical significance, however, because the number of patients requiring supplemental oxygen was similar in both groups. The clinical

importance of transient saturation of less than 90% is not known.

We deliberately included two types of surgical procedures in this study. Patients who have undergone strabismus surgery are not expected to have an blood in their pharynx, whereas those who have undergone T/A may have blood or bloody secretion in the pharynx during the postoperative period. We wanted to determine whether extubation during deep anesthesia after T/A leads to more airway related complications than extubation after strabismus surgery. We also expected a higher incidence of laryngospasm and hemoglobin desaturation in group 2 patients who had undergone T/A and therefore had blood in the pharynx than in those undergoing strabismus surgery. Although there were no statistically significant differences between the two surgical subgroups, all three instances of laryngospasm occurred in patients who had undergone T/A. Two of these occurred in the operating room after extubation during deep anesthesia (Table 2) and the third, which also involved a patient who had undergone extubation during deep anesthesia, occurred in the recovery room (Table 3).

One obvious bias of this study is that patients in group 1 received 100% oxygen for 5 min before tracheal extubation, whereas patients in group 2 were maintained on 50% nitrous oxide until extubation and were given 100% oxygen for 5 min after extubation. Because oxygen was administered for 5 min in both groups but at different times, comparison of SpO₂ between the two groups is difficult. Desaturation in group 1 patients may have been due to bucking, coughing, and restlessness exhibited during awake extubation. Occasionally, acute arterial hypoxemia occurs during the patient's emergence from anesthesia due to transient right-to-left shunt (8,9).

Given the low incidence of complications, a second concern about a study such as ours is the possibility of a type II error. The number of patients studied must be adequate to detect small differences between the two techniques. The incidence of intraoperative laryngospasm is as high as 22% in children (4,10). If the incidence of laryngospasm would have been 22% compared with the observed 1.4%, a sample size of 35 patients per group would have provided a 75% chance to detect such a difference at the $P = 0.05$ level. Monroe et al. (11) have reported the incidence of postoperative sore throat in orotracheally intubated patients to be 30.9%–64.5%. In our study, if the proportion of patients with sore throat would have been 65% instead of the observed 30%, a sample size of 35 patients per group would have provided an 80% chance of detecting such a difference at a $P = 0.05$ level.

In conclusion, in healthy children undergoing elec

tive surgery, the preference of the anesthesiologist or surgical requirements may dictate the choice of extubation technique. Patients undergoing extubation when they are deeply anesthetized should be closely observed at least until they have regained consciousness and control of the airway reflexes. The anesthesiologist may observe the patient in the operating room until these criteria are satisfied; however, if a decision is made to observe the patient in the PACU, the skills and capabilities of the recovery room personnel have to be considered. Personnel skilled in airway management should be available to intervene should airway difficulty develop in the patient in the recovery room.

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Is Premedication With Oral Glycopyrrolate as Effective as Oral Atropine in Attenuating Cardiovascular Depression in Infants Receiving Halothane for Induction of Anesthesia?

Richard S. Cartabuke, MD, Patricia J. Davidson, MD, and Louise O. Warner, MD

Department of Anesthesiology, Children's Hospital, Columbus, Ohio

The authors conducted a double-blind study to compare premedication with oral glycopyrrolate and oral atropine in prevention of bradycardia and hypotension during induction of anesthesia with halothane-N₂O in 90 outpatient infants and children aged 1–18 mo who were randomized into three groups to receive either an oral placebo, oral atropine (0.02 mg/kg), or oral glycopyrrolate (0.05 mg/kg) approximately 1 h before induction of anesthesia. Heart rate and mean arterial pressure were measured

before drug administration, just before induction of anesthesia, and every minute until surgical stimulation occurred. Glycopyrrolate, at the dose used, was significantly less effective than atropine in attenuating bradycardia during induction; neither glycopyrrolate nor atropine altered the incidence or degree of hypotension. Antisialagogic activity and side effects were comparable, except for significantly more flushing with atropine.

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Halothane-N₂O is commonly used for induction of general anesthesia in infants and young children because of ease of administration and lack of airway irritability. However, halothane produces both dose-related (1) and age-related (2) cardiovascular depression, especially in neonates (3). In infants, the diminution in cardiac output can be attenuated by premedication with atropine administered either intramuscularly (4) or orally (2). Side effects of atropine premedication (such as flushing and irritability) are generally benign, but may increase patient discomfort and parental anxiety in some cases. Moreover, the strong vagolytic effect of atropine might cause an unwanted tachycardia in certain cardiac patients (5).

Glycopyrrolate is a synthetic quaternary ammonium compound with peripheral anticholinergic properties similar to those of atropine. Because of a positive charge, it crosses the blood-brain barrier to a limited extent and hence exhibits fewer central nervous system side effects than atropine, which is a tertiary amine and readily permeates lipid barriers.

Glycopyrrolate is purported to be a more effective antisialagogue than atropine, but less likely to cause significant tachycardia while simultaneously blocking bradyarrhythmias more effectively (6).

Comparisons of intravenous glycopyrrolate and intravenous atropine administered at induction of anesthesia in children in whom anesthesia was maintained with halothane-N₂O have demonstrated similar cardiac protective effects (7,8). Oral glycopyrrolate has been suggested as an acceptable alternative anticholinergic premedication to oral atropine at doses five times parenteral doses to adjust for poor gastrointestinal absorption (5). However, there has been no evaluation of the efficacy of oral glycopyrrolate in the infant population (Berry FA, personal communication). We designed this randomized, double-blind, placebo-controlled study to answer the question: would oral glycopyrrolate, 0.05 mg/kg, be just as effective as oral atropine, 0.02 mg/kg, for cardiac protection and antisialagogic activity in infants undergoing induction of anesthesia with halothane, but without the side effects of undue tachycardia, flushing, or irritability?

Methods

This study was approved by the Human Subjects Research Committee of Columbus Children's Hospital, and informed parental consent was obtained for

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Address correspondence to Dr. Cartabuke, Department of Anesthesiology, Children's Hospital, 700 Children's Drive, Columbus, OH 43205.

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each candidate. Participants consisted of full-term infants and young children between 1 and 18 mo of age, ASA physical status I or II and without known cardiac or pulmonary disease, who were scheduled for elective outpatient surgical procedures requiring general anesthesia. Ninety patients were randomly assigned to one of three oral premedication groups: group 1 patients received a placebo, group 2 patients received 0.02 mg/kg of atropine, and group 3 patients received 0.05 mg/kg of glycopyrrolate. The dosages of atropine and glycopyrrolate were chosen on the basis of a previously published recommendation (5). The drugs were dissolved in a flavored syrup solution and dispensed in coded syringes by the pharmacy. All solutions were administered by a registered nurse in the short stay unit approximately 60 min before the scheduled time of surgery. The code was not revealed until the study was completed. Before drug administration, baseline heart rate (HR) and mean arterial pressure (MAP) were recorded (Dinamap).

Just before parental separation in the holding area, the patient was observed for the presence or absence of flushing and irritability. In the operating room, an electrocardiographic pad and an appropriately sized blood pressure cuff were applied and preinduction HR and MAP (Dinamap) were recorded. Oxygen saturation was measured by a Nellcor oximeter. Anesthesia was induced with a 5-L flow consisting of 60% N₂O and 40% O₂, with the addition of incremental concentrations of halothane, to a maximum of 3% inspired. An intravenous catheter was inserted, if indicated, for the administration of fluids or drugs. Heart rate and MAP were measured at 1-min intervals during induction and up to the time of surgical stimulation. At the time of insertion of the oral airway, the presence or absence of oropharyngeal secretions was noted. Intravenous atropine was administered for bradycardia during induction at the discretion of the attending anesthesiologist. Postoperatively, the patient was monitored in a standard fashion in the postanesthesia care unit and reevaluated for flushing and generalized irritability/delirium.

Tabulated data consisted of age, weight, duration of fasting, the time between administration of the oral solution and induction of anesthesia, maximum halothane concentration, and HR and MAP measurements (baseline, preinduction, and lowest before surgical stimulation). Incidences of bradycardia (defined as >20% decrease in HR compared with baseline [predrug] levels) and hypotension (>30% decrease in MAP compared with preinduction levels) were recorded, as well as incidences of satisfactory antisialagogic effect and preinduction and postanesthetic flushing and irritability.

Statistical significance ($P < 0.05$) between groups was determined by one-way analysis of variance for

Table 1. Patient Characteristics

	Placebo (n = 31)	Atropine (n = 31)	Glycopyrrolate (n = 25)
Age (mo)	10.4 ± 4.8	11.4 ± 3.8	11.3 ± 3.9
Weight (kg)	8.9 ± 2.0	9.4 ± 1.5	9.6 ± 1.7
Duration of fasting (h)	9.1 ± 2.6	10.2 ± 2.3	9.3 ± 2.6
Time between premedication and induction (min)	46.2 ± 20.7	53.2 ± 25.0	56.6 ± 18.3
Maximum inspired concentration of halothane (%)	2.7 ± 0.4	2.9 ± 0.4	2.8 ± 0.2

Values are mean ± SD.

age, weight, duration of fasting, the time between premedication and induction, and maximum halothane concentration. The statistical significance of differences in HR and MAP between groups was tested by one-way analysis of covariance with repeated measures, using the Newman-Keuls test for post-hoc analysis. χ^2 Values were used for between groups analysis of categorical data.

Results

Data from 87 of 90 infants eligible for the study were analyzed: one patient in each group was excluded because of violations in either the premedication or induction protocols. A pharmacy violation of the double-blind coding during the study necessitated rerandomization and resulted in an uneven group distribution: group 1, $n = 31$; group 2, $n = 31$; and group 3, $n = 25$. There were no significant differences among the three groups in age, weight, duration of fasting, time between administration of the oral solution and induction of anesthesia, or maximum halothane concentration (Table 1).

Baseline HRs were also comparable (Table 2). Preinduction (after drug) HR increased significantly over baseline (before drug) HR in all three groups but was not significantly different among the three groups. Infants given atropine had the greatest increase (23.0%) in HR, and those receiving glycopyrrolate the least (10.8%). The increase in HR in the placebo group averaged 15.1%. During induction, HR was best maintained in the atropine group: although the lowest HR measurement in that group was significantly lower than preinduction HR, it was not significantly different from baseline HR. Moreover, the lowest HR in the atropine group was significantly higher than in either the placebo or glycopyrrolate group. Lowest HRs within the placebo and glycopyrrolate groups were significantly lower than both baseline and preinduction measurements (Table 2).

Table 2. Heart Rate and Mean Arterial Pressure Data

	Placebo (n = 31)	Atropine (n = 31)	Glycopyrrolate (n = 25)
Heart rate (beats/min)			
Baseline	129.3 ± 17.9	127.6 ± 17.1	132.1 ± 14.5
Preinduction	148.8 ± 22.6 ^a	157.0 ± 31.6 ^a	146.4 ± 26.6 ^a
Lowest	110.0 ± 20.9 ^b	125.9 ± 26.6 ^c	102.1 ± 14.2 ^b
Mean arterial pressure (mm Hg)			
Baseline	72.5 ± 13.1	72.4 ± 15.3	79.9 ± 19.7
Preinduction	82.2 ± 27.6	86.2 ± 26.3 ^a	80.1 ± 22.3
Lowest	51.5 ± 10.5 ^b	56.4 ± 13.4 ^b	55.9 ± 9.7 ^b

Values are mean ± SD.

^aSignificantly above baseline levels and lowest levels (within groups).

^bSignificantly below baseline levels and preinduction levels (within groups).

^cSignificantly higher than in placebo and glycopyrrolate groups.

The incidence of bradycardia in the atropine group (14.8%) was significantly lower than in either the placebo (39.3%) or glycopyrrolate (66.7%) group; the difference between placebo and glycopyrrolate groups was close to being significant ($P = 0.0545$). No infant in the atropine group was given intravenous atropine during induction of anesthesia. Three patients in each of the other two groups were treated for bradycardia with intravenous atropine.

Baseline MAPs were comparable among the three groups (Table 2). Preinduction MAP in the atropine group was a significant 19.1% above baseline levels; MAP increases in the placebo and glycopyrrolate groups were 13.4% and 0.25%, respectively. Lowest MAP levels in all three groups were significantly below baseline and preinduction measurements, but were not significantly different among the three groups (Table 2). The incidence of hypotension (placebo = 61.5%, atropine = 65.4%, glycopyrrolate = 47.6%) was not significantly different in the three groups.

Before induction, the incidence of flushing was significantly greater in the atropine group (26.7%) than in the glycopyrrolate group (4.0%) but not in the placebo group (10.0%). Frequency of irritability was comparable among the three groups (placebo = 30.0%, atropine = 46.7%, glycopyrrolate = 52.0%). The incidence of flushing and irritability in the post-anesthesia care unit was not appreciably different from preinduction levels. The incidence of complete drying of oropharyngeal secretions was significantly greater in the glycopyrrolate group (40.9%) than in the placebo group (15.4%) but was not significantly different from the atropine group (25.9%).

Discussion

The oral route for premedication in children has proved to be both acceptable and efficacious (9). Preoperative medication is used in children (a) to

provide sedation and tranquility, (b) to supplement general anesthesia techniques, (c) to decrease airway secretions, and (d) to block unwanted autonomic responses. At our institution, drugs administered to achieve the first two effects (sedatives/hypnotics and anxiolytics) are not commonly used in infants and children less than 18 mo of age because of the wide range of pharmacokinetic and pharmacodynamic responses and the high incidence of undesirable post-operative side effects, such as respiratory depression, prolonged sedation, and delirium. However, anticholinergics may be useful in infants to accomplish the third and fourth objectives: they are excellent drying agents and effectively protect against bradycardia associated with anesthetic drugs and airway manipulation (5).

Sensitivity to the myocardial depressant effects of halothane varies inversely with age (2,3,10). Increased negative inotropy with halothane in the very young has been attributed to age-related differences in anesthetic potency and/or myocardial structure (11) and to a more rapid uptake and distribution of halothane with more rapid achievement of myocardial concentrations (12). Increased negative chronotropy with halothane may be due to a depressed baroreceptor response to hypotension (13,14) and vagal predominance (15) in the very young. The less compliant infant heart, with a reduced contractile mass (16), depends more on an increase in HR than on an increase in stroke volume to compensate for a decreased cardiac output (14) and is better able to accomplish this during halothane anesthesia in the presence of an anticholinergic drug.

For this study, oral doses of atropine and glycopyrrolate were based on the recommendation of a twofold and fivefold increase, respectively, over intravenous doses (5); articles addressing pharmacokinetics and pharmacodynamics have generally used like doses (17,18). Our study demonstrated that pre-

medication with 0.02 mg/kg of oral atropine attenuated the bradycardia associated with halothane anesthesia in infants and young children, confirming the results of Miller and Friesen (2). Oral glycopyrrolate, 0.05 mg/kg, was ineffective in maintaining HR. This is probably due to the fact that, in contrast to atropine, gastrointestinal absorption of glycopyrrolate is variable and incomplete. Indeed, Ali-Melkkilä et al. (17) concluded that the oral route (in older adults receiving approximately 0.05 mg/kg of glycopyrrolate) is of no value as a routine premedication. However, they did find a significant antisialagogic effect with oral glycopyrrolate, even at low plasma concentrations: evidently, much higher plasma concentrations are needed to produce tachycardia, possibly due to different sensitivities of muscarinic receptor subtypes to glycopyrrolate (19). Results of our study support this supposition: patients in the glycopyrrolate group exhibited a significant antisialagogic effect compared with placebo, but no HR effect. In fact, oral glycopyrrolate actually provided *less* protection from bradycardia compared with placebo. This may reflect a weak peripheral muscarinic cholinergic agonist effect associated with small doses (low plasma concentrations) of anticholinergic drugs (20).

Oral atropine was less effective in this study in maintaining MAP than in maintaining HR, which also corroborates the study of Miller and Friesen (2). Barash et al. (1) used echocardiography to show that even 0.02 mg/kg of intravenous atropine administered during halothane anesthesia in children did not reverse ventricular depression or increase blood pressure significantly but did improve cardiac output and all rate-dependent variables. It would seem that anticholinergics have little effect in ameliorating negative inotropy associated with halothane.

The majority of infants in this study underwent myringotomy with or without insertion of tympanostomy tubes. Anesthesia for this procedure is generally provided using a face mask without an intravenous line because of its brevity. In the nonatropinized infant in whom insertion of an intravenous line is not planned, a "window of vulnerability" for bradycardia occurs between the times of mask placement and surgical stimulation. Oral atropine premedication can virtually close this window.

In summary, oral premedication with 0.05 mg/kg of glycopyrrolate was significantly less effective than oral premedication with 0.02 mg/kg of atropine in attenuating bradycardia during induction of halothane anesthesia in infants and young children 1-18 mo of age. Neither drug affected the incidence or degree of hypotension. Atropine caused significantly more flushing than glycopyrrolate, but increases in HR before induction of anesthesia, antisialagogic

effect, and the incidence of irritability were not significantly different.

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Resistance to Vecuronium in Patients With Cerebral Palsy

S. S. Moorthy, MD, Gopal Krishna, MD, and Stephen F. Dierdorf, MD

Department of Anesthesia, Riley Children's Hospital, Indiana University Medical Center, Indianapolis, Indiana

To determine the electromyographic response of patients with cerebral palsy to vecuronium, 10 children (mean age, 6 yr 10 mo) without cerebral palsy and 11 children with cerebral palsy (mean age, 10 yr 3 mo) were studied. All patients were undergoing abdominal or orthopedic surgery and were anesthetized with isoflurane and nitrous oxide. The time from intravenous administration of 0.1 mg/kg of vecuronium to

25% recovery of control twitch height was 43.9 ± 5.3 and 18.9 ± 1.7 min (mean \pm SEM) in children without and with cerebral palsy, respectively ($P < 0.01$). The authors conclude that patients with cerebral palsy are either resistant to vecuronium or have a rapid clearance as evidenced by the rapid recovery from neuromuscular blockade.

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Patients with upper motor neuron lesions (1,2), burns (3), and adult respiratory distress syndrome (4) are resistant to nondepolarizing muscle relaxants (NDMR). Disuse atrophy (5) and immobilization (6) in experimental animals is associated with decreased sensitivity to NDMR. In addition, patients treated with carbamazepine (7), phenytoin (8), corticosteroids (9), and aminophylline (10) for their coexisting diseases have decreased sensitivity to NDMR. We observed that children with cerebral palsy required more NDMR during surgery as compared with normal children. The present study was designed to evaluate the electromyographic response of patients with cerebral palsy to vecuronium.

Methods

The study was approved by the institutional review board and informed consent was obtained from the parents or guardians of the patients. Ten children (mean age, 6 yr 10 mo) belonging to ASA class I or II who were undergoing elective surgery served as controls. Eleven children with cerebral palsy (mean age, 10 yr 3 mo) belonging to ASA class II or III who were undergoing abdominal or orthopedic procedures were included in the study. These patients had spasticity in all their extremities.

After intravenous atropine (10 μ g/kg) and thiopen-

tal (5 mg/kg) were administered for induction of anesthesia, the patients were allowed to breathe spontaneously, inhaling a mixture of 39% oxygen, 60% nitrous oxide, and 1% isoflurane through a face mask. The electrodes for the electromyographic monitor (Datex Relaxograph, Datex Instrumentation Corp., Helsinki, Finland) were placed according to the manufacturer's recommendation (the stimulating electrodes on the median nerve in the forearm and the monitoring electrodes on the thenar muscles). The thenar muscle electromyographic (EMG) responses were obtained using 0.15-ms supramaximal pulses at 0.1 Hz for train-of-four responses that were recorded on a paper at slow speed. Five minutes after induction, a control EMG response was obtained and 0.1 mg/kg of vecuronium was administered rapidly at the hub of the indwelling intravenous catheter. The trachea was intubated when maximum twitch depression occurred or the twitch response disappeared. Anesthesia was maintained using oxygen (39%), nitrous oxide (60%), and isoflurane (1%) as monitored by an Ohmeda multigas analyzer (Ohmeda 6000 Multigas Monitor; Ohmeda, Madison, Wis.). End-tidal carbon dioxide was monitored by the multigas analyzer and was maintained between 35 and 40 mm Hg. Patient temperature was monitored using a temperature probe incorporated into an esophageal stethoscope and was maintained between 36 and 37°C. The recovery times of the first twitch of the train of response (T1) from the time of administration of vecuronium to 25% and 50% recovery compared with the control twitch height were calculated from the recording paper. The recovery times to 75% and 100% were not calculated because of readministration of muscle relaxants to most of the chil-

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Address correspondence to Dr. Moorthy, 1120 South Drive, Fesler Hall 204, Indianapolis, IN 46202-5115.

Table 1. Recovery Times to 25% and 50% of First Twitch (T) of the Train-of-Four Electromyographic Recordings in Normal Children and Children With Cerebral Palsy

	T1-25 (min)	T1-50 (min)
Normal children (<i>n</i> = 10)	43.9 ± 5.3	55.5 ± 7.0
Children with CP		
All, <i>n</i> = 11	18.9 ± 1.1 (<i>P</i> < 0.01)	23.4 ± 2.3 (<i>P</i> < 0.01)
Phenytoin-treated, <i>n</i> = 5	17.4 ± 2.3 (<i>P</i> < 0.01)	21.6 ± 3.4 (<i>P</i> < 0.01)
Phenobarbital-treated, <i>n</i> = 6	20.17 ± 1.1 (<i>P</i> < 0.01)	25.0 ± 0.9 (<i>P</i> = 0.02)

CP, cerebral palsy; T1-25, time to 25% recovery from the control height of the first twitch; T1-50, time to 50% recovery from the control height of the first twitch.

Probability is calculated by comparing children with cerebral palsy to normal children.

Values are mean ± SEM.

dren. Statistical analysis was done by using an unpaired *t*-test between normal patients and patients with cerebral palsy.

Results

The T1 recovery time to 25% of the control (T1-25) was 43.9 ± 5.3 min (mean ± SEM) in normal children, whereas in children with cerebral palsy it was 18.9 ± 1.7 min (*P* < 0.01) (Table 1). The T1 recovery time to 50% of the control (T1-50) was 55.5 ± 7.0 min in normal children and 23.4 ± 2.3 min in children with cerebral palsy. All of the children with cerebral palsy had a history of seizures and were receiving anti-seizure medications. Five of these children were receiving phenytoin and six children were being treated with phenobarbital. The T1-25 and T1-50 in the children with cerebral palsy receiving phenytoin were 17.4 ± 2.3 and 21.6 ± 3.4 min, respectively. The T1-25 and T1-50 in phenobarbital-treated children were 20.2 ± 1.1 and 25.0 ± 0.9 min, respectively.

Discussion

Our findings demonstrate that patients with cerebral palsy are resistant to the neuromuscular blocking effects of vecuronium. This resistance was evidenced by the short recovery time of the first twitch (T1) of train-of-four EMG responses to 25% (T1-25) and 50% (T1-50) of the control response of T1 (Table 1, Figures 1 and 2). We also have indirect evidence that patients with cerebral palsy may require greater doses of vecuronium to produce complete loss of twitch response (Figure 2).

Patients with upper motor neuron disease and hemiplegia are resistant to NDMR (1,2). Shayeitz and Matteo (9) demonstrated resistance to metocurine in both spastic and normal limbs of hemiplegic patients. It can be speculated that this resistance in normal limbs is secondary to cross-innervation by pyramidal tracts. In the same study, Shayeitz and Matteo also found that monitoring thumb twitch may underestimate the degree of neuromuscular blockade in the muscles of respiration. The exact mechanism of the resistance of patients with upper motor neuron lesions is, as yet, unclear. The resistance to NDMR may be secondary to an increase in the number of junctional and extrajunctional acetylcholine receptors. Brett et al. (10) demonstrated an increased number of acetylcholine receptors in muscle samples from patients with multiple sclerosis.

All our patients with cerebral palsy were severely affected with spastic quadriplegia, mental retardation, and seizure disorders. Other causes of resistance to NDMR that conceivably could have affected our patients include immobilization with muscle atrophy (4,5) and concomitant administration of phenytoin (7) and phenobarbital. Proposed mechanisms for such drug interactions include (a) increased metabolism of the muscle relaxant via hepatic enzyme induction, (b) decreased sensitivity of muscle receptors to the muscle relaxant, (c) increased numbers of

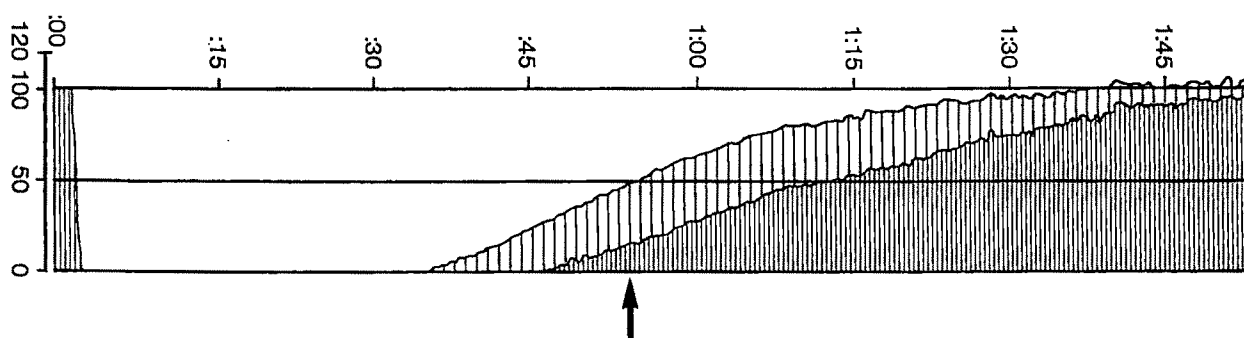


Figure 1. Electromyographic train-of-four responses in a normal patient after administration of 0.1 mg/kg of vecuronium for tracheal intubation. The x-axis represents time in minutes, the y-axis the twitch height, widely separated bars the first twitch (T1), and narrowly separated bars the fourth twitch (T4). The arrow points to T1-50. (Redrawn for clarity.)

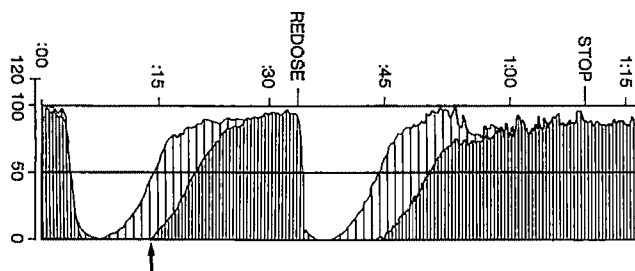


Figure 2. Vecuronium (0.1 mg/kg) in a patient with cerebral palsy demonstrating rapid recovery of T1-25 (10 min) and T1-50 (12 min). Redose, second dose of vecuronium; stop, end of surgery. The bottom arrow points to T1-50. Widely separated bars represent the first twitch (T1), and narrowly separated bars the fourth twitch (T4). (Redrawn for clarity.)

receptors, and (d) increased muscle end-plate cholinesterase activity. In our study five of the 11 children with cerebral palsy were being treated with phenytoin and six with phenobarbital. Phenytoin and other seizure medications can produce resistance to nondepolarizing muscle relaxants (7). However, phenobarbital is not known to alter the response to nondepolarizing muscle relaxants. In the present study both groups of children were found to be resistant to vecuronium, indicating that the children with cerebral palsy were resistant to vecuronium because of upper motor neuron damage.

We conclude that patients with cerebral palsy are resistant to vecuronium as evidenced by their rapid recovery from neuromuscular blockade. This increased rate of recovery was evidenced by use of a

peripheral EMG response. As recovery of respiratory muscles may not be as rapid as that of limb muscles, evidence of adequate respiratory muscle function must be assured before discontinuation of ventilatory support.

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Neuromuscular Effects of Succinylcholine on the Vocal Cords and Adductor Pollicis Muscles

Claude Meistelman, MD, Benoît Plaud, MD, and François Donati, PhD, MD, FRCPC

Service d'Anesthésie, Institut Gustave-Roussy, Villejuif, France; Department of Anaesthesia, McGill University, Montreal, Quebec, Canada

To quantify the effects of succinylcholine at the laryngeal adductor muscles and the adductor pollicis, 17 adult patients were studied during propofol-fentanyl anesthesia. Train-of-four stimulation was applied to the ulnar nerve at the wrist and the recurrent laryngeal nerve at the notch of the thyroid cartilage. Laryngeal response was measured as pressure changes in the cuff of the tracheal tube positioned between the vocal cords. The force of contraction of the laryngeal adductor muscles and of the adductor pollicis were compared after administration of 0.25 or 0.5 mg/kg of succinylcholine. With 0.25 mg/kg, maximum blockade of first twitch (T1) was $66\% \pm 10\%$ (mean \pm SEM) and $45\% \pm 13\%$ at the vocal cords and the adductor pollicis, respectively ($P < 0.01$). After

0.5 mg/kg, maximum blockade at the vocal cords ($93\% \pm 2\%$) and the adductor pollicis ($84\% \pm 6\%$) did not differ significantly. For both doses, time to maximal blockade was shorter for the vocal cords (0.9 ± 0.1 min) than for the adductor pollicis (1.7 ± 0.2 min; $P < 0.01$). Time to 90% recovery of T1 after a bolus of 0.5 mg/kg was similar at the vocal cords (4.3 ± 0.5 min) and the adductor pollicis (5.2 ± 0.8 min) (NS). The ED₅₀ was less at the laryngeal adductors (0.170 mg/kg) than at the adductor pollicis (0.278 mg/kg). It is concluded that, in adults, succinylcholine-induced blockade is more rapid and more intense at the laryngeal muscles than at the adductor pollicis.

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Succinylcholine is commonly used to facilitate tracheal intubation; paralysis of several muscle groups is necessary to obtain good intubating conditions. For example, the response of the diaphragm (1,2) and masseter (3) is different, both in intensity and time-course, from that of the commonly monitored adductor pollicis; and a discrepancy has been described between tracheal intubating conditions and the intensity of peripheral paralysis (4).

Adequate relaxation of the laryngeal adductor muscles is also required to obtain good tracheal intubating conditions. However, the effects of succinylcholine on the laryngeal adductor muscles are unknown because of the unavailability of a technique to measure the force of contraction of these muscles. A method was developed recently to assess the effects of muscle relaxants on the larynx (5).

Therefore, this study was designed to compare the onset time, maximum blockade, and duration of

action of a succinylcholine-induced neuromuscular blockade on both the laryngeal adductor and the adductor pollicis muscles.

Methods

The protocol was approved by our human ethics committee and informed consent was obtained from the patients. Seventeen patients, ASA physical status I or II, aged 18-70 yr and undergoing elective surgical procedures, were studied. No patient had any disease or metabolic abnormality known to alter neuromuscular transmission. Other exclusion criteria were the presence of an abnormal upper airway, laryngeal abnormalities, previous head and neck surgery, or radiotherapy. Patients who deviated from their normal body weight by more than 20% were also excluded, as were those taking any medication interfering with neuromuscular function.

No premedication was used. Anesthesia was induced with 2-5 μ g/kg of fentanyl and 2-3 mg/kg of propofol intravenously. After induction of anesthesia, tracheal intubation was performed without neuromuscular blocking drugs, using a Mallinckrodt tracheal tube (Athlone, Ireland; inner diameter 7.5 mm). No local anesthetic drug was given intratracheally.

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Address correspondence to Dr. Donati, Department of Anaesthesia, Royal Victoria Hospital, 687 Pine Avenue West, Montreal, Quebec, Canada H3A 1A1.

The midportion of the inflatable cuff of the tube was positioned between the vocal cords under direct vision. The cuff was inflated with air to a pressure of at least 10–12 mm Hg and sufficient to prevent leaks. The cuff was connected to an air-filled Hewlett-Packard pressure transducer. Ventilation was controlled mechanically to maintain the partial pressure of CO₂ (Pco₂), as measured by capnography, between 30 and 40 mm Hg. Then, anesthesia was maintained with a continuous infusion of propofol (10–15 mg·kg⁻¹·h⁻¹) and intermittent boluses of fentanyl (1–2 µg/kg). Neither halogenated anesthetics nor nitrous oxide was used.

The ulnar nerve was stimulated at the wrist with surface electrodes, using 2-Hz train-of-four stimulation every 10 s with 0.2-ms supramaximal square-wave stimuli. The force of contraction of the adductor pollicis was measured with a Curamètre Module 2 Transducer (Bio-Industry, France) and recorded on paper. Bilateral adduction of the vocal cords was produced by supramaximal stimulation of the recurrent laryngeal nerve. A negative cutaneous electrode was placed on the notch of the thyroid cartilage, and the positive electrode was placed either on the sternum or the forehead. Supramaximal train-of-four stimulations were applied every 10 s with a Curamètre Module 1 (Bio-Industry) nerve stimulator. Vocal cord response was determined by measuring the pressure change produced in the cuff of the tracheal tube by the adduction of the vocal cords. The response was displayed on an oscilloscope and recorded on paper.

After a stable baseline had been obtained, 0.25 (*n* = 8) or 0.5 (*n* = 9) mg/kg of succinylcholine was injected by random allocation as a rapid bolus. After maximal blockade was attained, the interval between train-of-four stimulations was increased to 20 s at each site of stimulation. Neuromuscular blockade was monitored until the first twitch response (T1) for both muscles recovered to at least 90% of control value. The following variables were measured: onset time (time from the end of injection until maximum T1 blockade) and the times from the injection to 25%, 50%, 75%, and 90% T1 recovery. The results are expressed as mean ± SEM. The results obtained at the larynx and the adductor pollicis were compared using Student's *t*-test for paired data. Linear regressions were obtained between the logit transformation of maximum T1 blockade and the logarithm of dose, and the ED₅₀ was derived for each muscle. The ED₅₀ values are given as estimate ± standard error of estimate for the mean. Analysis of covariance was used to compare the dose-response curves of the two muscles. A *P* value of 0.05 or less was considered to indicate statistically significant differences.

Table 1. Demographic Data

Dose (mg/kg)	Age (yr)	Height (cm)	Weight (kg)	Sex (M/F)
0.25	52 ± 3	159 ± 3	58 ± 3	1/7
0.50	46 ± 3	162 ± 2	56 ± 3	0/9

Values are mean ± SEM.

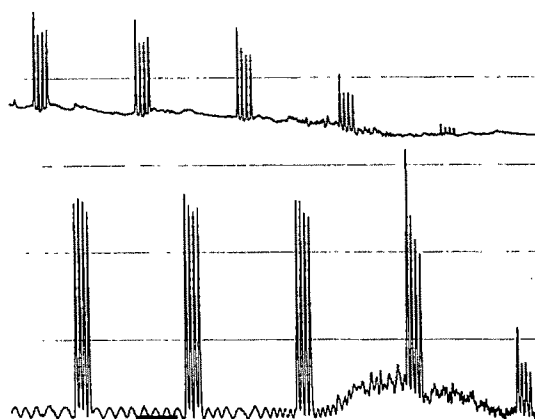


Figure 1. Response to train-of-four stimulation applied every 10 s of the recurrent laryngeal nerve (top) and ulnar nerve (bottom) after 0.5 mg/kg of succinylcholine (given at the solid horizontal bar). Laryngeal blockade is faster and more intense than adductor pollicis blockade. Twitch tension augmentation and increase in baseline tension are observed at the adductor pollicis but not at the larynx.

Results

Age, height, weight, and sex ratio were similar in both groups. Patients' demographic data are summarized in Table 1. A typical tracing is shown in Figure 1. With either dose, succinylcholine produced maximum blockade more rapidly on the vocal cords than on the adductor pollicis (Table 2, Figures 2 and 3). Maximum neuromuscular blockade was greater at the vocal cords for both doses, but statistical significance was achieved only for the lower dose (0.25 mg/kg). Recovery times could not be measured after administration of 0.25 mg/kg because maximum blockade was not intense enough. After administration of 0.5 mg/kg, recovery tended to occur 1 min earlier at the vocal cords, the difference being significant only for the times to 25% and 50% recovery (Table 3).

The dose-response curves for both muscles did not differ in slope (vocal cords = 3.13 ± 1.29; adductor pollicis = 4.29 ± 1.45), but the dose-response curve of the vocal cords was shifted to the left, as compared with the adductor pollicis. The ED₅₀ was (mean ± standard error of estimate for the mean) 0.170 ± 0.027 mg/kg at the vocal cord adductors and 0.278 ± 0.037 mg/kg at the adductor pollicis (*P* < 0.03).

In seven of the eight patients receiving 0.25 mg/kg

Table 2. Onset Characteristics

Dose (mg/kg)	Maximum blockade			Onset		
	Larynx (%)	Adductor pollicis (%)	<i>P</i>	Larynx (min)	Adductor pollicis (min)	<i>P</i>
0.25	66 ± 10	45 ± 13	0.01	0.9 ± 0.1	1.4 ± 0.1	0.01
0.50	93 ± 2	84 ± 6	NS	0.9 ± 0.1	1.7 ± 0.2	0.001

NS, not significant.
Values are mean ± SEM.

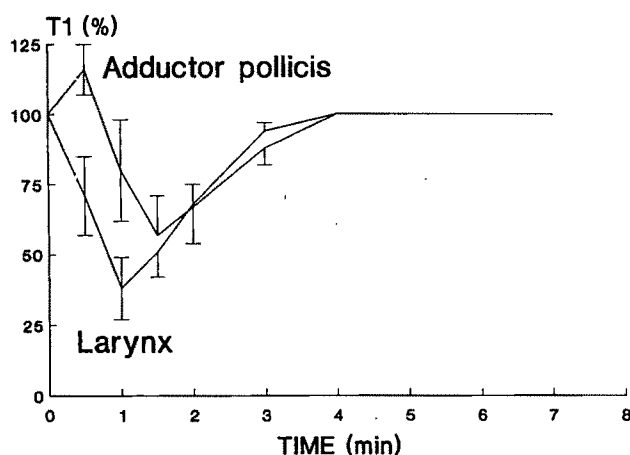


Figure 2. First twitch height (T1) at the larynx and adductor pollicis versus time after 0.25 mg/kg of succinylcholine.

of succinylcholine and five of the nine patients receiving 0.5 mg/kg, twitch tension augmentation (i.e., response greater than 105%) of the control value occurred at the adductor pollicis (Table 4 and Figure 1). Twitch tension augmentation was not present at the vocal cords. An increase in baseline tension was sometimes seen at the adductor pollicis (Figure 1), but this phenomenon was never observed at the larynx.

Discussion

We found that succinylcholine produces more rapid and more intense vocal cord neuromuscular blockade when compared with the adductor pollicis. This accelerated onset at the laryngeal muscles, compared with the adductor pollicis, has been reported previously in anesthetized humans receiving vecuronium (6). A shorter onset of action at other muscles (diaphragm, masseter) than at the adductor pollicis was also described in humans for both succinylcholine (2,3) and nondepolarizing muscle relaxants (2). An important factor governing onset of action is circulation time to muscle (7,8). Muscles close to the central circulation tend to have a greater blood flow and are paralyzed more rapidly than peripheral, more poorly

Table 3. Recovery Characteristics (after 0.5 mg/kg of succinylcholine)

	Larynx	Adductor pollicis	<i>P</i>
Time 25% (min)	2.1 ± 0.3	3.1 ± 0.5	0.05
Time 50% (min)	2.9 ± 0.3	3.8 ± 0.6	0.05
Time 75% (min)	3.7 ± 0.4	4.5 ± 0.7	NS
Time 90% (min)	4.3 ± 0.5	5.2 ± 0.8	NS

NS, not significant.
Values are mean ± SEM.

perfused muscles. Thus, the faster onset of blockade at the vocal cords might be related to their proximity to the aorta and to a higher blood supply than the peripheral muscles, favoring more rapid access of succinylcholine to the neuromuscular junction. Because the pattern of nerve stimulation can influence onset time (9), the same type of stimulation (TOF every 10 s) was used for both muscles.

Maximum blockade was significantly greater at the vocal cords compared with the adductor pollicis after administration of 0.25 mg/kg of succinylcholine. Statistical significance was not reached for the higher dose because blockade was close to 100%. The reasons for the increased sensitivity of laryngeal muscles are unclear. Blood flow might play a role. If onset time is short at the vocal cords because of a high blood flow, it follows that the vocal cords might receive a greater amount of succinylcholine than the adductor pollicis, thus enhancing blockade at the larynx. However, other factors must play a role.

Vecuronium neuromuscular blockade at the larynx was less intense than at the adductor pollicis, in spite of a faster onset at the larynx (6). In this respect, succinylcholine behaves differently. Also, succinylcholine spares the diaphragm, in spite of a fast onset at that muscle (1), indicating that the sensitivity of laryngeal adduction to succinylcholine is different from that of the diaphragm.

Some of these findings might be related to the different sensitivities of different fiber types and muscle relaxants (10,11). Laryngeal adductor muscles (lateral cricoarytenoid and thyroarytenoid) have short

Table 4. Twitch Tension Augmentation Expressed as Percent of Control

Dose	Twitch tension augmentation (%)	Time (min)
0.25	131 ± 9	0.66 ± 0.08
0.50	121 ± 8	0.56 ± 0.04

Values are mean ± SEM.

contraction times (12) but the adductor pollicis is made up mostly of slow oxidative fibers (13). Experimental data in cats (11,14) and pigs (15) suggest that, contrary to nondepolarizing blockers, succinylcholine was more effective in blocking the fast contracting tibialis than the slow contracting soleus muscle.

Selective stimulation of laryngeal adductor muscles was obtained in all patients. The method used is similar to the technique used in animals to control the position of the vocal cords (16) and to measure pressure changes within the glottis (17,18). The stimulating electrode was placed over the notch of the thyroid cartilage because the branch of the recurrent laryngeal nerve that innervates the laryngeal adductor muscles projects anteriorly (5). The use of nitrous oxide was avoided because of the possible diffusion of the gas into the inflatable cuff. Propofol and an opioid were used for induction and maintenance of anesthesia to avoid the possible drug interaction between succinylcholine and volatile agents.

Dose-response curves were obtained with two doses only. It is possible that three or four doses would have yielded more accurate data, but this could have created the problem of 0% and 100% responses, which cannot be treated with logit transformation. In addition, more accurate recovery data are obtained if a sufficient number of patients receive the same dose. Errors in constructing the dose-response curve with only two doses are possible, but this was preferred to a cumulative technique because, during administration of succinylcholine, redistribution and elimination are important factors that may induce underestimation of potency. Meretoja and Wirtavuori (19) have recently demonstrated that a good estimate of potency of muscle relaxants could be obtained with two doses. Previous studies have reported lower values of ED₅₀ than obtained here for succinylcholine at the adductor pollicis (0.11 [3] and 0.19 [20] mg/kg). However, in two recent studies where succinylcholine was given shortly after the induction agent and halogenated agents were avoided, the ED₅₀ was 0.31 (21) and 0.27 mg/kg (22), respectively. These results are similar to our findings of 0.278 mg/kg for the ED₅₀ at the adductor pollicis. Even if the technique used in this study should be

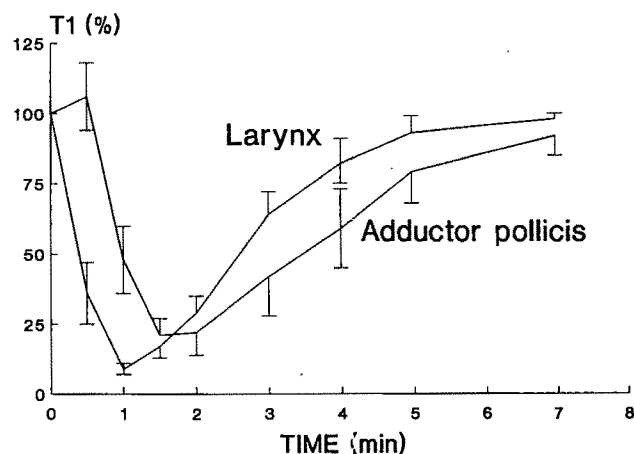


Figure 3. First twitch height (T1) at the larynx and adductor pollicis versus time after 0.5 mg/kg of succinylcholine.

interpreted with caution, the differences observed in ED₅₀ indicate that the adductor pollicis muscle is more resistant to succinylcholine than the laryngeal adductor muscles.

Twitch tension augmentation has been reported after administration of succinylcholine in animals (23) and humans (22,24). This increase has been attributed to a presynaptic mechanism. After a dose of 0.25 mg/kg, first twitch tension increased to 131% of control, similar to the recent results obtained by Szalados et al. (22) with the same dose. This phenomenon was not observed in any patient at the laryngeal adductor muscles. The reasons for the absence of twitch tension augmentation at laryngeal muscles are unclear but could be due to differences in the type of fibers of the two muscles studied. Succinylcholine also produces an increase in baseline tension, which has been reported at the masseter (3,25,26). Similar changes, but of smaller magnitude, were observed at the adductor pollicis in this and other studies (3,26). Such changes in baseline tension were not observed at the laryngeal muscles. These differences between muscles might be related to muscle type. However, these observations do not imply that twitch augmentation and changes in baseline tension have a common mechanism.

During onset of neuromuscular blockade, paralysis of the adductor pollicis lags behind relaxation of the laryngeal adductor muscles. These findings could explain the discrepancies observed between the intubating conditions and the degree of peripheral neuromuscular blockade (4). After injection of vecuronium, maximum blockade of vocal cords also occurs before maximum blockade of the adductor pollicis (6), but succinylcholine is different in two important respects. Maximum laryngeal blockade occurs in less than 1 min, compared with 3 min for vecuronium; and succinylcholine doses sufficient to block the

adductor pollicis are expected to produce paralysis of the vocal cords. For vecuronium, however, the laryngeal adductors require much more than the adductor pollicis for an identical degree of blockade. Therefore, in addition to its rapid onset of action, succinylcholine exhibits some selectivity for laryngeal adductor muscles, making this drug particularly suitable for tracheal intubation.

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Myocardial Oxygen Supply/Demand Relations During Phenylephrine Infusions in Dogs

George J. Crystal, PhD, Song-Jung Kim, MS, M. Ramez Salem, MD, and Mohamed Abdel-Latif, MD

Department of Anesthesiology, Illinois Masonic Medical Center, and the Departments of Anesthesiology and of Physiology and Biophysics, University of Illinois College of Medicine, Chicago, Illinois

Experiments were performed on 14 fentanyl-pentobarbital-anesthetized dogs to assess changes in myocardial oxygen supply/demand relations during intravenous infusions of phenylephrine ($2.8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Myocardial blood flow was measured with radioactive microspheres. Myocardial oxygen and lactate extraction were determined. Myocardial oxygen consumption was calculated with the Fick equation. In series 1, measurements were obtained during phenylephrine-induced pressor responses. In series 2, measurements were obtained with aortic pressure maintained constant with an extracorporeal reservoir during phenylephrine infusion, so that coronary vasomotor responses could be assessed in the absence of increases in ventricular afterload and perfusion pressure. In series 1, the phenylephrine-induced increase in mean aortic pressure (+42%) was accompanied by proportional (60%) increases in myocardial blood flow and myocardial oxygen consumption and with no change in the endocardium-to-epicardium

flow ratio, oxygen extraction, coronary sinus oxygen tension and oxygen saturation, or myocardial lactate extraction. In series 2, phenylephrine infusion caused a transmurally uniform 15% decrease in myocardial blood flow combined with a 10% decrease in myocardial oxygen consumption. The coronary arteriovenous oxygen difference increased modestly (+5%), resulting in small decreases in coronary sinus oxygen tension and oxygen saturation, whereas lactate extraction was unaffected. The present findings suggest that phenylephrine has a direct vasoconstrictor effect in the coronary circulation that is weak and completely overridden by metabolic autoregulatory mechanisms in response to pressure-induced augmentations in cardiac workload. The authors conclude that the myocardium is not at risk when phenylephrine is used to treat hypotension in patients with adequate cardiac function and coronary vasodilator reserve.

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The coronary circulation possesses α_1 -adrenoreceptors that mediate vasoconstriction during stimulation of the cardiac sympathetic nerves or during intracoronary administration of agonists (1). The potency of this vasoconstrictor mechanism is evidenced by its ability to limit coronary blood and myocardial oxygen delivery when it is opposed by metabolic vasodilation secondary to catecholamine-induced increases in myocardial metabolism (2), hemorrhagic hypotension (3), coronary stenosis (4), or exercise (5).

Intravenous infusions of phenylephrine, an α_1 -adrenoreceptor agonist, are widely used intraopera-

tively to treat hypotension by increasing systemic vascular resistance secondary to vasoconstriction in peripheral tissues (6). It is uncertain whether the plasma concentration of phenylephrine during such pressor infusions is sufficient to activate the coronary α_1 -adrenoreceptors. If so, this factor may impair the ability of metabolic vasodilator mechanisms to satisfy the pressure-induced increase in myocardial oxygen demand (7).

Accordingly, the authors sought to evaluate indices of the balance between myocardial oxygen supply and demand, including blood flow, oxygen consumption, and lactate extraction, during phenylephrine-induced pressor responses in fentanyl-pentobarbital-anesthetized dogs. In addition, measurements were obtained with aortic pressure maintained constant during phenylephrine infusion to evaluate coronary vasomotor responses in the absence of increases in ventricular afterload and aortic pressure and of decreases in heart rate.

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Address correspondence to Dr. Crystal, Department of Anesthesiology, Illinois Masonic Medical Center, 836 West Wellington Avenue, Chicago, IL 60657.

Methods

Experimental Preparation

The experimental protocols were conducted in compliance with the Institutional Animal Research Committee. Experiments were performed on 14 conditioned, heartworm-free mongrel dogs of either sex (weight range, 20–25 kg). Anesthesia was induced with intravenous bolus injection of fentanyl (40 $\mu\text{g}/\text{kg}$) and pentobarbital (10 mg/kg). Anesthesia was maintained by continuous intravenous infusion of fentanyl and pentobarbital at rates of 20 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ and 1 mg $\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$, respectively. After tracheal intubation and left thoracotomy in the fourth intercostal space, the dog was mechanically ventilated (Air Shields, Inc.) with inspired oxygen fraction equal to 1.0. The volume and rate of the ventilator were established to maintain arterial carbon dioxide tension (Paco_2) at physiologic levels. Muscle paralysis was obtained with an intravenous injection of 0.1 mg/kg of vecuronium bromide with supplements at 0.05 mg $\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$.

Polyethylene cannulas were inserted into (a) the thoracic aorta through the left femoral and right brachial arteries for monitoring aortic blood pressure and for obtaining samples of arterial blood for analysis of gas composition and (b) the right femoral vein for intravenous injections and infusions. The heart was exposed through a left thoracotomy in the fourth intercostal space. A polyethylene cannula was inserted into the left atrium through the left atrial appendage for injecting radioactive microspheres. A micromanometer-tipped pressure transducer (Millar Instruments, Houston, Tex.) was inserted into the left ventricle through the left atrium and the mitral valve to measure left ventricular pressure. The maximum rate of rise of left ventricular systolic pressure ($\text{dP}/\text{dt max}$) was obtained from the left ventricular pressure pulse with an electronic differentiator. The left ventricular pressure signal was used to drive a cardiometer. A noncannulating electromagnetic flow transducer was placed around the ascending aorta to measure cardiac output (less coronary blood flow) using an electromagnetic flowmeter (Narco Biosystems, Houston, Tex.). Heparin (400 U/kg) was administered intravenously after surgery to prevent blood coagulation.

Aortic pressure was measured with a Statham transducer (model P23ID; Gould, Cleveland, Ohio) and was averaged electronically. A permanent record of monitored hemodynamic parameters was obtained with a Gould recorder (model 2800S; Gould, Cleveland, Ohio). Systemic vascular resistance was computed by dividing mean aortic pressure by mean aortic blood flow.

Experimental Measurements

Regional myocardial blood flow. Regional myocardial blood flow was measured with $15 \pm 3 \mu\text{m}$ microspheres labeled with the γ -emitting radionuclides ^{141}Ce , ^{51}Cr , ^{46}Sc , ^{85}Sr , and ^{113}Sn (New England Nuclear Corp., Boston, Mass.; 3M Company, St. Paul, Minn.). Before injection, the microspheres were dispersed in a solution of 10% dextran and were agitated in a vortex mixer and in an ultrasonic bath. Approximately 1×10^6 microspheres were administered for each flow determination. The microspheres were flushed into the left atrium over 30 s with 5 mL of body-temperature isotonic saline solution. Administration of microspheres had no detectable effect on monitored hemodynamic parameters. Beginning simultaneously with each microsphere injection, duplicate reference arterial samples were collected at a rate of 6 mL/min for 3 min through two cannulas of different lengths inserted into the aorta through the right femoral artery. Radioactivities of the duplicate reference samples differed by less than 10%, indicating adequate mixing of microspheres in the left ventricular output. Autologous blood obtained before the study was simultaneously infused during the reference sample withdrawal to maintain isovolemic conditions.

After the final injection of microspheres, the heart beat was stopped by intravenous injection of KCl and the heart was excised, trimmed of adipose tissue, valves and great vessels, and frozen to facilitate transmural sampling. Full-thickness myocardial samples were obtained from the left and right ventricular artery free wall and interventricular septum. The samples from the left ventricular artery free wall and septum were cut into thirds transmurally and those from the right ventricular artery free wall into halves transmurally to yield regional samples. All myocardial samples contained in excess of the 400 microspheres required to ensure high-precision, low-error flow estimates (8). Each section was transferred to a tared counting tube. The myocardial and reference blood samples were weighed and analyzed for radioactivity with a gamma scintillation counter equipped with a multichannel analyzer (model 1282-002; LKB, Turku, Finland). Isotope separation was accomplished by standard techniques of gamma spectroscopy. Values for myocardial blood flow (MBF in $\text{mL}\cdot\text{min}^{-1}\cdot 100\text{ g}^{-1}$) were calculated from the equation

$$\text{MBF} = \text{ABF} \times (\text{MC}/\text{AC}) \times 100,$$

where ABF is the rate of arterial reference sampling (mL/min), MC is microsphere radioactivity ($\text{counts}\cdot\text{min}^{-1}\cdot\text{g}^{-1}$) in the tissue samples, and AC is the total microsphere radioactivity (counts/min) in the arterial reference samples. Values for MBF within

each heart wall were averaged to compute a value for mean transmural blood flow.

Myocardial oxygen consumption. A polyethylene cannula was positioned in the coronary sinus through the right jugular vein and the right atrium for collecting samples of venous effluent from the perfusion field of the left coronary artery. One-milliliter blood samples were simultaneously collected anaerobically from the aorta and the coronary sinus to determine the left coronary arteriovenous oxygen difference. Hemoglobin concentration and percent hemoglobin saturation of blood samples were measured with a CO-oximeter (model 482; Instrumentation Laboratories, Lexington, Mass.) and were used to calculate oxygen bound to hemoglobin assuming an oxygen carrying capacity for hemoglobin of 1.39 mL O₂/g (9). The oxygen dissolved in the blood was computed (O₂ dissolved = 0.003 mL O₂·100 mL blood⁻¹·mm Hg⁻¹) and was added to the bound component to compute total oxygen content.

Myocardial oxygen uptake (MVO₂) (in mL·min⁻¹·100 g⁻¹) was calculated from the Fick equation:

$$MVO_2 = MMBF \times [(a-v)O_2 \text{ difference}/100],$$

where MMBF is the arithmetic mean myocardial blood flow for the left ventricular samples in each heart (mL·min⁻¹·100 g⁻¹) and (a-v)O₂ difference is the coronary arteriovenous oxygen difference (vol %). Paired 1-mL blood samples were obtained from the aorta and coronary sinus and were analyzed for plasma lactate concentration using an enzymatic method (Paramax Analytical System, Baxter, Irvine, Calif.). These values were used to compute percent myocardial lactate extraction.

Experimental Protocols

Series 1. Phenylephrine-induced pressor response (n = 12). The dogs were permitted to stabilize for at least 30 min after surgical preparation before baseline hemodynamic measurements were obtained. Then phenylephrine (concentration, 40 µg/mL in saline solution) was infused at a rate of 2.8 µg·kg⁻¹·min⁻¹, which was sufficient to increase mean aortic pressure by approximately 50%. After attainment of steady state hemodynamic conditions during phenylephrine infusion (approximately 10 min), a second set of hemodynamic measurements was obtained.

Series 2. Constant aortic pressure (n = 7). Increased aortic pressure itself influences coronary blood flow by raising coronary perfusion pressure and by altering primary determinants of cardiac work demand, i.e., afterload and heart rate (1). To eliminate these complicating factors during phenylephrine in-

fusion, studies were performed with aortic pressure maintained constant. A 500-mL glass reservoir was connected to the cannulated left subclavian artery with wide-bore tubing. Reservoir pressure was maintained equal to mean aortic pressure with compressed gas. During intravenous infusion of phenylephrine (2.8 µg·kg⁻¹·min⁻¹), vascular constriction caused blood to be translocated from the dog's circulation to the reservoir, allowing aortic pressure to be maintained equal to control pressure.

As in series 1, control measurements were obtained when monitored hemodynamic parameters were stable. Phenylephrine infusion was then initiated and subsequent measurements were obtained when reservoir volume peaked (approximately 10 min), thus indicating that pressor mechanisms were maximally activated. The average peak reservoir volume was 364 ± 41 mL. Five dogs participating in both series 1 and 2 received duplicate phenylephrine infusions, with and without controlled pressure. In these dogs, the order of these conditions was varied to avoid experimental bias. At least 1 h was allowed for recovery from a phenylephrine infusion before a second infusion was initiated.

Effects of phenylephrine were evaluated using the Student's *t*-test for paired samples (10). A *P* < 0.05 was considered significant throughout this study.

Results

Series 1. Phenylephrine-Induced Pressor Response

Phenylephrine infusion increased mean aortic pressure (+42%) and systemic vascular resistance (+65%), and decreased heart rate (-25%) and aortic blood flow (-17%) (Table 1). Aortic blood values were unchanged except that oxygen tension (Po₂) decreased modestly (Table 1). Myocardial blood flow increased by approximately 60% in left ventricular wall, right ventricular wall, and septum, without changing its transmural distribution (Table 2). The increase in blood flow in the left ventricular wall was proportional to the increase in myocardial oxygen consumption resulting in no change in the arteriovenous oxygen difference, percent oxygen extraction, coronary sinus Po₂, or coronary sinus oxygen saturation (Table 3). Lactate extraction also was not affected by phenylephrine infusion.

Series 2. Constant Aortic Pressure

With aortic pressure controlled, phenylephrine infusion decreased aortic blood flow (-25%) and increased systemic vascular resistance (+28%), whereas left ventricular dP/dt max and aortic blood values were constant (Table 1). Myocardial blood flow decreased mod-

Table 1. Effect of Intravenous Infusion of Phenylephrine on Systemic Hemodynamic Parameters^a

	Increased MAP		Constant MAP	
	Control	Phenylephrine	Control	Phenylephrine
MAP (mm Hg)	107 ± 5	152 ± 10 ^b	106 ± 4	105 ± 5
Heart rate (beats/min)	121 ± 8	91 ± 6 ^b	115 ± 9	122 ± 8
Aortic blood flow (L/min)	1.8 ± 0.2	1.5 ± 0.1 ^b	1.6 ± 0.2	1.2 ± 0.1 ^b
LV dP/dt max (mm Hg/s)	1976 ± 102	1908 ± 106	1842 ± 118	1758 ± 96
Systemic vascular resistance (mm Hg·L ⁻¹ ·min ⁻¹)	58 ± 4	96 ± 4 ^b	72 ± 10	92 ± 10 ^b
Aortic blood values				
Po ₂ (mm Hg)	228 ± 40	189 ± 38 ^b	270 ± 47	209 ± 46
Pco ₂ (mm Hg)	37 ± 1	37 ± 1	35 ± 1	35 ± 2
pH	7.40 ± 0.01	7.38 ± 0.01	7.41 ± 0.01	7.40 ± 0.01
O ₂ content (vol%)	21.0 ± 0.7	21.5 ± 0.7	21.1 ± 0.8	20.7 ± 0.8
O ₂ saturation (%)	96.2 ± 0.5	95.6 ± 0.9	97.0 ± 0.7	96.0 ± 1.5
Hematocrit (%)	46 ± 2	47 ± 2	44 ± 2	44 ± 2
Lactate (mEq/L)	1.7 ± 0.2	1.9 ± 0.2	1.4 ± 0.2	1.6 ± 0.2

LV, left ventricular; MAP, mean aortic pressure; Po₂, oxygen tension; Pco₂, carbon dioxide tension; SVR, systemic vascular resistance.

Values are mean ± SE.

^aA 2.8-μg·kg⁻¹·min⁻¹ infusion of phenylephrine was administered with MAP permitted to increase or held constant.^bP < 0.5 from control values.**Table 2.** Effect of Intravenous Infusion of Phenylephrine on Regional Myocardial Blood Flows^a

	Increased MAP		Constant MAP	
	Control	Phenylephrine	Control	Phenylephrine
Left ventricular wall				
Epicardium	59 ± 6	95 ± 7 ^b	69 ± 7	57 ± 4 ^b
Midmural	56 ± 4	87 ± 9 ^b	60 ± 6	53 ± 5 ^b
Endocardium	62 ± 5	101 ± 10 ^b	65 ± 5	56 ± 5 ^b
Mean	59 ± 5	94 ± 8 ^b	65 ± 6	55 ± 4 ^b
Endo/Epi	1.1 ± 0.1	1.1 ± 0.1	0.9 ± 0.1	1.0 ± 0.1
Right ventricular wall				
Epicardium	42 ± 6	68 ± 10 ^b	33 ± 3	31 ± 3 ^b
Endocardium	45 ± 7	73 ± 11 ^b	35 ± 4	34 ± 4
Mean	43 ± 6	71 ± 10 ^b	34 ± 3	32 ± 4 ^b
Endo/Epi	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 1.1	1.1 ± 0.1
Septum				
Right ventricle	47 ± 5	73 ± 12 ^b	45 ± 7	40 ± 5 ^b
Midmural	61 ± 5	93 ± 14 ^b	59 ± 8	52 ± 6 ^b
Left ventricle	64 ± 6	99 ± 13 ^b	65 ± 11	55 ± 8 ^b
Mean	57 ± 5	88 ± 13 ^b	56 ± 8	49 ± 6 ^b
LV/RV	1.4 ± 0.1	1.5 ± 0.1	1.4 ± 0.1	1.4 ± 0.1

MAP, mean aortic pressure; endo, endocardium; epi, epicardium; LV, left ventricle; RV, right ventricle.

Values are mean ± SE.

^aPhenylephrine was infused at a rate of 2.8 μg·kg⁻¹·min⁻¹ with MAP permitted to increase or held constant. Blood flow was measured in mL·min⁻¹·100 g⁻¹.^bP < 0.5 from control values.

estly in all regions (left ventricular wall, -15%; right ventricular wall, -6%; and septum, -13%) without change in the transmural distribution of blood flow (Table 2). The decrease in left ventricular blood flow was accompanied by a reduction in myocardial oxygen consumption (-10%), which resulted in modest increases in the arteriovenous oxygen difference (+5%) and oxygen extraction (+6%) and modest decreases in coronary sinus Po₂ (-10%), oxygen saturation (-15%),

and oxygen content (-16%) (Table 3). Myocardial lactate extraction was unaffected.

Discussion

The increase in myocardial oxygen consumption within the left ventricular wall during phenylephrine-induced hypertension (series 1) indicated that the increase in cardiac work demand due to augmented

Table 3. Effect of Intravenous Infusion of Phenylephrine on Parameters of Left Ventricular Myocardial Oxygen Supply/Demand Balance^a

	Increased MAP		Constant MAP	
	Control	Phenylephrine	Control	Phenylephrine
Blood flow (mL·min ⁻¹ ·100 g ⁻¹)	59 ± 5	94 ± 8 ^b	65 ± 6	55 ± 4 ^b
O ₂ consumption (mL·min ⁻¹ ·100 g ⁻¹)	8.2 ± 0.4	13.2 ± 1.5 ^b	8.9 ± 0.8	8.0 ± 0.6 ^b
(a-v)O ₂ difference (vol%)	14.3 ± 0.9	13.9 ± 0.6	14.1 ± 0.9	14.8 ± 2.0 ^b
Oxygen extraction (%)	67 ± 2	65 ± 1	67 ± 3	71 ± 3 ^b
Lactate extraction (%)	50 ± 5	56 ± 3	56 ± 8	58 ± 6
Coronary sinus blood values				
Po ₂ (mm Hg)	27 ± 1	29 ± 1	29 ± 1	26 ± 1 ^b
Pco ₂ (mm Hg)	52 ± 2	52 ± 2	50 ± 3	49 ± 2
pH	7.33 ± 0.01	7.33 ± 0.01	7.33 ± 0.02	7.35 ± 0.01
O ₂ content (vol%)	7.2 ± 0.5	7.7 ± 0.4	7.0 ± 0.5	5.9 ± 0.6 ^b
O ₂ saturation (%)	34 ± 3	35 ± 1	33 ± 3	28 ± 3 ^b
Lactate (mEq/L)	0.9 ± 0.1	0.9 ± 0.1	0.6 ± 0.1	0.6 ± 0.1

MAP, mean aortic pressure; (a-v)O₂, arteriovenous oxygen; Po₂, oxygen tension; Pco₂, carbon dioxide tension.

Values are mean ± SE.

^aA 2.8-μg·kg⁻¹·min⁻¹ infusion of phenylephrine was administered with MAP permitted to increase or held constant.^bP < 0.5 from control values.

afterload overrode the decrease due to the baroreceptor-mediated reduction in heart rate (7). Myocardial blood flow increased in proportion to the increased oxygen consumption, which resulted in no change in oxygen extraction, coronary sinus Po₂ and oxygen saturation, or lactate extraction. These findings suggest that direct coronary vasoconstriction through the α₁-adrenoreceptors did not impair maintenance of myocardial oxygen supply/demand balance by local metabolic mechanisms (1).

Physical distention of coronary vessels probably contributed little to increased blood flow in the left ventricular wall during phenylephrine-induced pressor responses as the perfusion pressures attained were within the autoregulatory range in this region (11). However, this was likely not the case in the right ventricular wall where pressure-flow autoregulation is much less developed because of the greater tendency for distention of intracardiac coronary vessels to stretch the surrounding myocardial fibers, i.e., the so-called "garden-hose effect" (12). This effect increases cardiac performance secondary to a Frank-Starling mechanism, which augments myocardial oxygen demand leading to a metabolically mediated rise in blood flow. Previous findings demonstrating the effect of coronary perfusion pressure itself on blood flow in the right ventricular wall (12) suggest that the increase in perfusion pressure during phenylephrine infusion in series 1 was sufficient to account entirely for the rise in right ventricular blood flow.

In contrast to the findings in series 1, Woodman and Vatner (13) demonstrated pronounced coronary vasoconstriction, as indicated by a relatively constant blood flow in the face of an approximate doubling of mean aortic pressure, during intravenous infusions

of phenylephrine in conscious dogs pretreated with ganglionic (hexamethonium), β-adrenoreceptor (propranolol), and muscarinic (atropine) antagonists. The accentuated coronary vasoconstrictor responses in the study of Woodman and Vatner were likely due to the combined influence of two factors: (a) absence of the depressive influence of general anesthesia on contractile activity of vascular smooth muscle (14), and (b) ability of propranolol to potentiate α-receptor-mediated coronary vasoconstrictor responses (15).

With aortic pressure constant, phenylephrine infusion caused consistent but small (maximum 15%) decreases in myocardial blood flow indicating modest coronary vasoconstriction. In the left ventricular myocardium, this coronary vasoconstriction could not be attributed exclusively to a direct pharmacologic effect as myocardial oxygen consumption decreased 10% presumably because venous return and cardiac output were reduced by displacement of blood into the extracorporeal reservoir (7). Metabolic mechanisms would be expected to reduce coronary blood flow in proportion to this reduction in myocardial oxygen consumption (1). Thus, these mechanisms would account for a significant portion of decreased myocardial blood flow evident in series 2. The magnitude of the direct coronary vasoconstrictor effect is reflected in the degree to which phenylephrine caused an imbalance between myocardial oxygen supply and demand, i.e., in the increases in arteriovenous oxygen difference and in the resultant decreases in coronary sinus Po₂ and oxygen saturation (1). The observed 5% increase in the arteriovenous oxygen difference is consistent with a very small direct coronary vasoconstrictor effect during phenylephrine infusion in the present study. It is noteworthy

that this direct constrictor effect did not reduce myocardial lactate extraction or convert it to production. This suggests that intramyocardial Po_2 was not decreased sufficiently to stimulate anaerobic metabolism (16).

The present findings under constant pressure conditions are consistent with previous investigations using different approaches to study direct coronary effects of α_1 -adrenoreceptor agonists in anesthetized animals. Mark et al. (17) injected phenylephrine into an extracorporeal perfusion circuit providing blood simultaneously to the left circumflex, cranial tibia (paw), and gracilis (muscle) arteries of dogs anesthetized with chloralose-urethane. As blood flow was maintained constant with a pump, changes in perfusion pressure reflected changes in vascular resistance. Mark et al. demonstrated minimal increases in perfusion pressure in the coronary bed (6 ± 3 mm Hg) compared with the paw and muscle beds (131 ± 16 and 83 ± 8 mm Hg, respectively). Gwartz and Stone (15) reported that intracoronary bolus injections of phenylephrine had no vasoconstrictor effects in pentobarbital-anesthetized dogs. Chilian et al. (18) found that intravenous infusions of norepinephrine (a combined α_1 - and α_2 -agonist) with systemic hemodynamics controlled and β -adrenergic receptors blocked with propranolol caused heterogeneous vasomotor responses within the epicardial coronary microcirculation of the pentobarbital-anesthetized cat as viewed by intravital microscopy; constriction occurred in arterial and arteriolar vessels greater than $100 \mu\text{m}$ in diameter, whereas autoregulatory dilation predominated in the smaller arteriolar vessels. The lack of norepinephrine effects on distal microvessels (in which approximately 50%–60% of total coronary resistance occurs [19]) is in keeping with the small direct vasoconstrictor effects of phenylephrine observed in series 2.

The present study was performed using fentanyl-vecuronium anesthesia to simulate human intraoperative conditions (20). The additional pentobarbital was dictated by the exorbitant quantities of fentanyl alone required to achieve a stable anesthetic state in dogs (21).

In conclusion, the present study demonstrated a direct vasoconstrictor action of phenylephrine in the coronary circulation that was weak and completely overridden by metabolic vasodilator factors in response to pressure-induced augmentations in cardiac workload. Although the present findings apply specifically to the conditions of the present study, e.g., the fentanyl-pentobarbital-vecuronium-anesthetized dog with a normal heart, they suggest that the myocardium is not at risk when phenylephrine is used to treat hypotension intraoperatively as long as

cardiac function and coronary vasodilator reserve are adequate.

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Is Dantrolene Safe to Administer in Sepsis?

The Effect of Dantrolene After Endotoxin Administration in Dogs and Rats

David S. Beebe, MD, Kumar G. Belani, MBBS, MS, Stephen E. Tuohy, BA,
Michael F. Sweeney, MD, Kristin Gillingham, MS, Vijaya Komanduri, MS, and
Richard J. Palahniuk, MD

Department of Anesthesiology, University of Minnesota, Minneapolis, Minnesota

Hyperthermia from septic shock may be indistinguishable from malignant hyperthermia. Dantrolene may be given in septicemia if the diagnosis is unclear. To determine if dantrolene is safe to use in sepsis, two studies were performed. In study 1, 18 anesthetized dogs in which profound septic shock was induced with 5 mg/kg of intravenous *Escherichia coli* endotoxin were randomized to receive (30 min later) intravenous injections of 10 mg/kg of dantrolene solution, the diluent of dantrolene, or maintenance intravenous fluids alone. The use of dantrolene solution and the diluent of dantrolene resulted in similar but transient statistically significant increases in the cardiac filling pressures and cardiac outputs and decreases in the vascular resistances compared with

the control dogs. In a second study, 185 rats were randomized into five equal groups. Groups 1, 2, and 3 received 15 mg/kg of intraperitoneal *Escherichia coli* endotoxin followed 30 min later by 10 mg/kg of dantrolene solution, the diluent of dantrolene, or normal saline. Groups 4 and 5 received normal saline followed by dantrolene or normal saline. The survival of groups 1, 2, and 3 was less at 24 h ($P < 0.0001$) than that of either control group, but was not significantly different from one another. The results suggest dantrolene can be administered safely under clinical conditions where the cause of hyperthermia and shock cannot clearly be ascribed to malignant hyperthermia or septicemia.

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Successful management of malignant hyperthermia (MH) requires early recognition and diagnosis followed by prompt initiation of therapy including the intravenous administration of dantrolene (1). Initial symptoms of MH include tachycardia, hyperventilation, skeletal muscle rigidity, fever, hypotension, and cyanosis after stress or the administration of certain drugs used in anesthesia that can trigger an attack of MH (2). The clinical presentation of MH may be indistinguishable from that of septicemia (3). Further confusion may arise when bacteremia is present before surgery, or with the intraoperative production of bacteremia associated with drainage of an abscess, infected kidney, or bowel manipulation. Determination of susceptibility to MH requires a muscle biopsy and halothane-caffeine contracture test (4). However, dantrolene must be administered early in an MH episode to be effective (1),

before muscle testing could possibly be performed. Thus, because the distinction between sepsis and MH is often difficult or impossible, it may be necessary to administer dantrolene in the presence of intraoperative hyperthermia without a definitive diagnosis of its cause (3).

It has never been determined if the use of dantrolene has any unrecognized adverse effects when septicemia is present. Experimental evidence suggests dantrolene acts intracellularly by inhibiting release of calcium from the sarcoplasmic reticulum of skeletal muscle, thereby producing a marked reduction in muscle contraction to electrical or pharmacologic stimulation without affecting action potential patterns (5). Dantrolene thus depresses the in vitro contractility of dog (6), rat (7), and cat (6) cardiac muscle as well as the diaphragm of the rat (7), while having no effect on the cardiovascular or respiratory systems of the intact dog at normal doses (<10 mg/kg) (8). In swine, intermediate doses of dantrolene (7.5 mg/kg) have no adverse cardiovascular effects (9), whereas larger doses (>9.9 mg/kg) cause severe myocardial depression (10). A distur-

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Address correspondence to Dr. Beebe, Department of Anesthesiology, B515 Mayo Box 294, 420 Delaware Street SE, Minneapolis, MN 55014.

bance of calcium homeostasis has also been implicated in the pathophysiology of septic shock (11-13). In addition, severe myocardial depression has been noted in human (14,15), rat (16), and canine (17,18) endotoxic shock.

The purpose of this study was to determine if dantrolene is safe to administer in septic shock. The clinician, faced with a patient with fever and shock caused by MH or septicemia, may then better judge whether dantrolene should be given and know what effect dantrolene will have on a patient in septic shock. To help the clinician predict the acute hemodynamic and metabolic effects of the administration of dantrolene to a patient in septic shock, the hemodynamic and metabolic effects of dantrolene were studied in anesthetized dogs in profound endotoxic shock. To help determine the effect of dantrolene on mortality in patients with sepsis, the effect of dantrolene on the 24-h survival of rats in endotoxic shock was studied.

Methods

Study 1

After obtaining animal care committee approval, 18 mongrel dogs weighing 19.1 ± 1.8 kg (sd) were randomly divided into three groups of six dogs each. After an overnight fast, each dog was anesthetized with 30 mg/kg of intravenous pentobarbital and paralyzed with 0.1 mg/kg of pancuronium. Anesthesia and paralysis were maintained with the infusion of $5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of pentobarbital and 0.05 mg/kg of pancuronium every 2 h. All dogs also received 10 mL/kg of lactated Ringer's solution followed by $4 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ of lactated Ringer's solution for maintenance fluids, as well as 100 U/kg of heparin intravenously to prevent clotting of blood in intravascular catheters. The trachea was intubated and the lungs were ventilated with a volume cycled ventilator (Siemens-Elma 900B servo) at a rate of 10 breaths/min and an initial fraction of inspired O_2 of 0.3. Tidal volume was adjusted to maintain a partial arterial pressure of CO_2 between 35 and 45 mm Hg and the fraction of inspired O_2 was adjusted to maintain a partial arterial pressure of O_2 greater than 90 mm Hg. Arterial and venous catheters were placed in the right femoral vessels and advanced to the distal aorta and inferior vena cava. A 2-mm (inside diameter) feeding tube was inserted into the bladder. A balloon-tipped pulmonary artery catheter (Swan-Ganz catheter model 93A-131-7F, American Edwards Laboratory) was advanced into the pulmonary artery through the right external jugular vein. The position was confirmed by intravascular pressure waveforms. Cardiac output was measured by the thermodilution technique

with 5 mL of cold ($<2^\circ\text{C}$) 5% dextrose in water solution at end expiration, taking the average of four measurements. Intravascular pressures were continuously measured and recorded with a Hewlett Packard 7834C monitor and 78576A recorder. Arterial and pulmonary venous blood gas tensions and pH values were measured. Arterial and venous hemoglobin saturations were corrected for temperature and pH using the equations described by Rossing and Cain (19).

Before endotoxin administration, the following baseline measurements were made in all dogs: mean arterial pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, right atrial pressure, cardiac output, blood temperature, arterial and mixed venous oxygen tensions, serum levels of sodium, potassium, and chloride, pH, blood glucose levels, and hemoglobin and blood ionized calcium levels. *Escherichia coli* endotoxin (ET) (lipopolysaccharide W. E. coli 055:B5, Difco), 5 mg/kg, was injected intravenously over 1 min. Zero time (T_0) was taken as the start of this injection. Measurements and laboratory values were repeated 30 min after ET administration (T_{30}). Dogs in group S received maintenance fluids only. At T_{30} dogs in group D received 10 mg/kg of dantrolene sodium, 1.5 g/kg of mannitol, and 30 mL/kg of sterile H_2O with pH adjusted to 9.5 by sodium hydroxide (NaOH) over 30 min in five divided doses. Dogs in group M received 1.5 g/kg of mannitol and 30 mL/kg of sterile H_2O with pH adjusted to 9.5 with NaOH in five divided doses over 30 min. Measurements and laboratory values were then repeated at T_{60} . Hemodynamic measurements were then repeated every 30 min and laboratory values every hour for the next 3 h. Total urine output was measured at T_{240} and the animals were killed.

Stroke volume (SV), systemic and pulmonary vascular resistances, left (LVSW) and right (RVSW) ventricular stroke work, and oxygen delivery (O_2 del) and uptake (Vo_2) were calculated by standard formulas (20). Cardiac output, SV, LVSW, RVSW, O_2 del, and Vo_2 were referred to the weight of each dog.

Statistical comparisons were carried out by one-way analysis of variance for between-group comparisons with Bonferroni's correction for multiple comparisons and *t*-tests for paired data. Statistical significance was determined as $P < 0.05$. Results are expressed as mean \pm sd.

Study 2

After obtaining animal care committee approval, 185 male Sprague-Dawley rats (BioLab, St. Paul, Minn.) weighing 350-450 g were randomly divided into five groups of 37 rats each. Animals in groups 1, 2, and 3 were given a single intraperitoneal (IP) injection of

15 mg/kg of ET (lipopolysaccharide *W. E. coli* 055:B5, Difco) with a 23-gauge needle using sterile technique over a 15-s period. Animals in groups 4 and 5 (the control groups) were given the same volume of 0.9% saline instead of ET. Animals were then returned to their individual cages and allowed free movement and access to food and water.

Thirty minutes after receiving the IP injection of either ET or saline, animals assigned to groups 1 and 4 were given IP injections of dantrolene solution containing 10 mg/kg of dantrolene sodium, 1.0 g/kg of mannitol, and 20 mL/kg of sterile H₂O with pH adjusted to 9.5 with NaOH. This solution of dantrolene was more concentrated (0.5 vs 0.33 mg/mL) than commercially available dantrolene normally used for patients to allow for the IP injection of 10 mg/kg without using excessive volumes. Animals assigned to groups 2 and 5 received IP injections of the same volume of 0.9% saline as controls. Animals assigned to group 3 received the diluent solution (M) of IP dantrolene containing 1.0 g/kg of mannitol and 20 mL/kg of sterile H₂O with pH adjusted to 9.5 with NaOH.

Observations were repeated at 2, 4, 6, 12, and 24 h after injection of either ET or saline. Animals were observed for activity level, alertness, respiratory rate, and stool quality to verify systemic illness. Survival was determined at 24 h after initial injections.

Survival data for each group were compared with that of other groups using Gehan's test. The level of statistical significance was $P < 0.05$.

Results

Study 1

With ET administration, there were significant decreases in the arterial pressures, cardiac filling pressures, and cardiac outputs in all three groups of dogs (Figures 1-3). With the administration of dantrolene, there was an immediate increase in the filling pressures, cardiac output, LVSW, and RVSW and a decrease in the systemic and pulmonary vascular resistances. Administration of the diluent solution (M) produced similar changes (Figures 1-3), and there were no significant differences in hemodynamics between the dantrolene and diluent solutions. The improvement proved transient with both dantrolene and diluent administration and by 1 h (T₁₂₀) there were no significant differences in the hemodynamics among the three groups.

Similarly, ET administration resulted in a significant decline in O₂ del in all three groups without changing Vo₂ significantly (Figure 4). Both dantrolene and the diluent solution resulted in a transient improvement in O₂ del without a significant

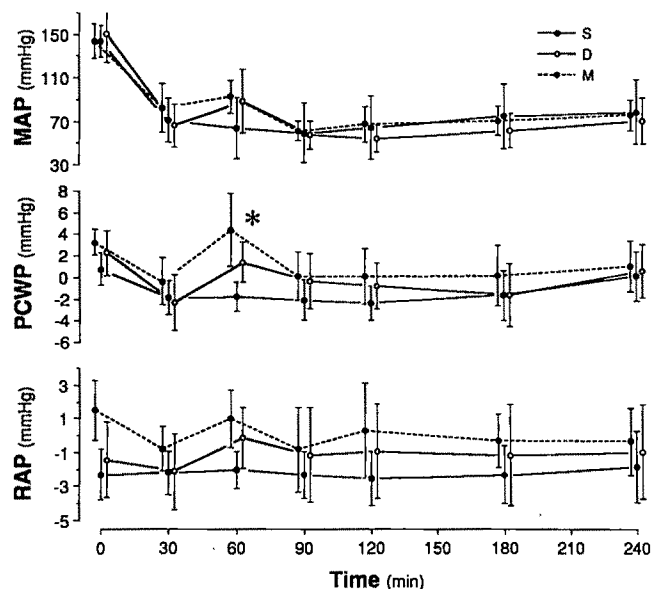


Figure 1. Mean arterial pressure (MAP), pulmonary capillary wedge pressure (PCWP), and right atrial pressure (RAP) in dogs given endotoxin at T₀ and then given maintenance fluids alone (S), dantrolene solution (D), or the diluent solution of dantrolene (M) from T₃₀ to T₆₀. * $P < 0.05$ for M and D compared with S.

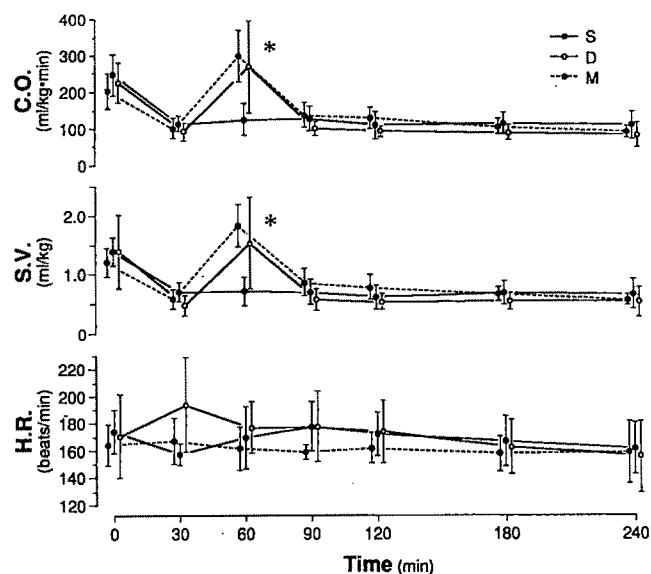


Figure 2. Cardiac output (CO), stroke volume (SV), and heart rate (HR) over time in the three groups of animals. Dogs given endotoxin at T₀ and then given maintenance fluids alone (S), dantrolene solution (D), or the diluent solution of dantrolene (M) from T₃₀ to T₆₀. * $P < 0.05$ for M and D compared with S.

change in Vo₂. There also were no significant differences in the temperatures among the three groups at any time interval, and ET administration did not result in a temperature elevation in any group (Figure 5).

The urine output of the dogs receiving dantrolene

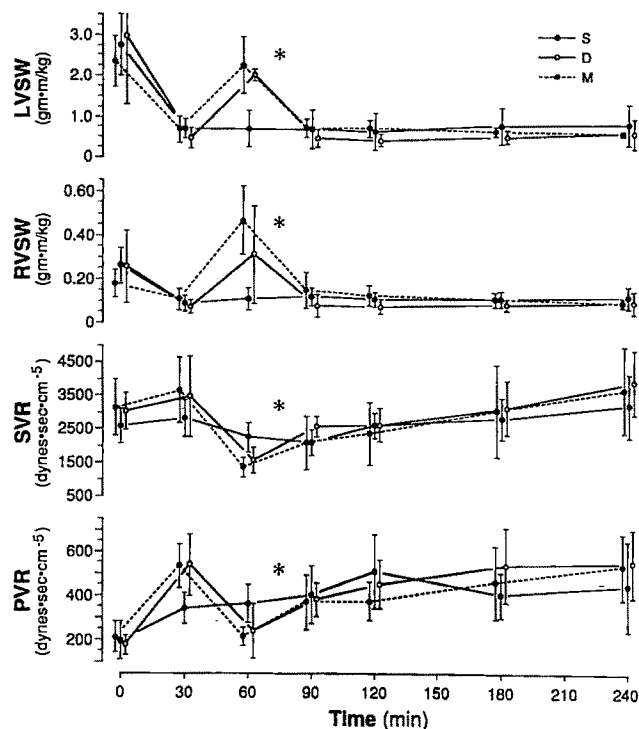


Figure 3. Left ventricular stroke work (LVSF), right ventricular stroke work (RVSW), systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) over time in the three groups of animals. Dogs given endotoxin at T_0 and then given maintenance fluids alone (S), dantrolene solution (D), or the diluent solution of dantrolene (M) from T_{30} to T_{60} . * $P < 0.05$ for M and D compared with S.

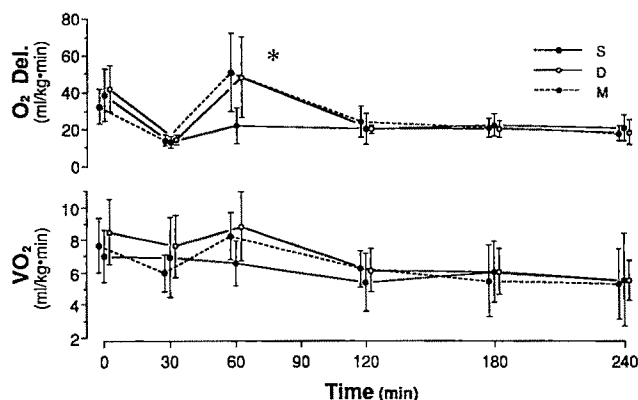


Figure 4. Oxygen delivery (O_2 del) and oxygen uptake (VO_2) over time in the three groups of animals. Dogs given endotoxin at T_0 and then given maintenance fluids alone (S), dantrolene solution (D), or the diluent solution of dantrolene (M) from T_{30} to T_{60} . * $P < 0.05$ for M and D compared with S.

(109 ± 112 mL) and diluent solution (188 ± 135 mL) tended to be greater than that of the septic-alone group receiving maintenance fluids only (40 ± 32 mL) but did not achieve statistical significance.

Administration of ET resulted in a similar degree of acidosis and hyperglycemia in all three groups

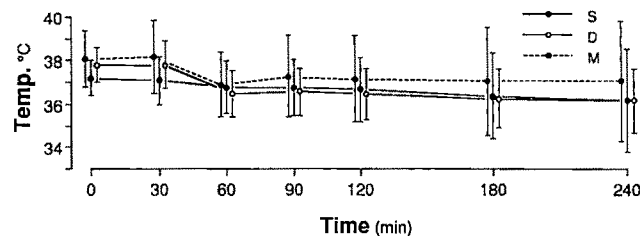


Figure 5. Blood temperature over time in the three groups of animals. Dogs given endotoxin at T_0 and then given maintenance fluids alone (S), dantrolene solution (D), or the diluent solution of dantrolene (M) from T_{30} to T_{60} . * $P < 0.05$ for M and D compared with S.

(Table 1). Administration of dantrolene solution or the diluent solution resulted in significant decreases in both the serum sodium (Na^+) and total calcium (Ca). Ionized calcium (ion Ca) levels declined slightly with dantrolene administration, but no values were outside the normal range. In contrast, the serum potassium (K^+) levels were higher after dantrolene administration than they were in the diluent and control groups. Hemoglobin concentration showed a steady increase after ET administration in the S group. Administration of dantrolene or the diluent solution resulted in a transient decline in the hemoglobin concentration at T_{60} in both groups.

Study 2

All rats in groups 1, 2, and 3 given ET showed clinical signs of sepsis. Within 30 min after IP injection of ET, rats became progressively lethargic and less interested in their surroundings. More than half of the rats developed tachypnea (RR 100-130), and the majority had diarrhea. These findings are consistent with previously described patterns of sepsis in laboratory models (21,22). In contrast, the animals in groups 4 and 5 that received saline instead of ET were all alert, active, and without tachypnea or diarrhea.

There were no deaths after 24 h in the control groups 4 and 5 that did not receive ET (Figure 6). Survival rates in all three groups given ET were significantly worse than in the control groups ($P < 0.0001$ for each of groups 1, 2, and 3 compared with groups 4 and 5). The 24-h survival of groups 1 (32%), 2 (32%), and 3 (46%) were not significantly different from one another.

Discussion

Clinicians may be faced with the dilemma of whether to administer dantrolene to a patient with hyperthermia when the cause of the fever could be septicemia

Table 1. Biochemical Data

Variable	Group	T ₀	T ₃₀	T ₆₀	T ₁₂₀	T ₂₄₀
Na ⁺ (mmol/L)	S	148 ± 4	144 ± 3 ^a	146 ± 6	145 ± 5	145 ± 5
	D	147 ± 2	143 ± 2	124 ± 2 ^{b,c}	130 ± 3 ^{b,c}	131 ± 3 ^{b,c}
	M	148 ± 3	146 ± 5	130 ± 3 ^{b,c}	134 ± 3 ^{b,c}	139 ± 6 ^c
K ⁺ (mmol/L)	S	3.3 ± 0.2	3.8 ± 0.6	2.6 ± 0.4 ^b	2.7 ± 0.6 ^b	3.5 ± 0.6
	D	3.4 ± 0.3	3.9 ± 0.4	3.7 ± 0.5 ^d	4.6 ± 1.3 ^d	5.4 ± 1.3 ^d
	M	3.4 ± 0.3	4.0 ± 0.7	3.1 ± 0.4 ^b	3.2 ± 0.9 ^b	3.7 ± 1.0
Total Ca (mg/dL)	S	10.2 ± 0.6	9.7 ± 0.6 ^a	9.3 ± 0.4	9.8 ± 0.6	9.3 ± 0.9
	D	10.0 ± 0.7	9.7 ± 0.7	7.8 ± 0.8 ^{b,c}	3.9 ± 0.8 ^{b,c}	8.4 ± 0.9 ^b
	M	10.0 ± 0.4	9.8 ± 0.3	8.1 ± 0.488 ^{b,c}	9.0 ± 0.6 ^b	8.7 ± 0.9 ^b
Ionized Ca (mmol/L)	S	1.26 ± 0.08	1.31 ± 0.07 ^a	1.28 ± 0.09	1.25 ± 0.08 ^b	1.27 ± 0.06
	D	1.21 ± 0.05	1.20 ± 0.06 ^c	1.07 ± 0.07 ^{b,e}	1.10 ± 0.09 ^{b,e}	1.08 ± 0.06 ^{b,e}
	M	1.25 ± 0.07	1.30 ± 0.06	1.20 ± 0.04 ^b	1.25 ± 0.06	1.22 ± 0.05 ^b
pH units	S	7.42 ± 0.06	7.32 ± 0.07 ^a	7.19 ± 0.05 ^b	7.16 ± 0.09 ^b	7.22 ± 0.10 ^b
	D	7.42 ± 0.04	7.29 ± 0.08 ^a	7.19 ± 0.06 ^b	7.18 ± 0.06 ^b	7.32 ± 0.04
	M	7.40 ± 0.03	7.24 ± 0.07 ^a	7.18 ± 0.05 ^b	7.18 ± 0.07	7.23 ± 0.10
Glucose (mg/dL)	S	93 ± 23	159 ± 21 ^a	215 ± 48 ^b	147 ± 46	104 ± 18 ^b
	D	94 ± 12	163 ± 36 ^a	232 ± 53 ^b	168 ± 51	97 ± 51 ^b
	M	101 ± 59	171 ± 48	168 ± 33	123 ± 16	94 ± 20 ^b
Hemoglobin (g/dL)	S	11.7 ± 2.4	12.6 ± 2.5	14.0 ± 2.0 ^b	15.2 ± 2.5 ^b	15.4 ± 2.8 ^b
	D	13.7 ± 1.0	16.5 ± 1.6 ^a	14.1 ± 1.8	17.2 ± 1.2	17.8 ± 1.3
	M	12.0 ± 2.2	15.9 ± 2.9 ^a	13.0 ± 2.9 ^b	15.3 ± 2.9	16.2 ± 3.3

S, endotoxin + maintenance fluids; D, endotoxin + dantrolene solution; M, endotoxin + diluent solution of dantrolene.

^a*P* < 0.05 for T₃₀ compared with T₀.

^b*P* < 0.05 for T₆₀, T₁₂₀, or T₂₄₀ compared with T₃₀.

^c*P* < 0.05 for D or M < S.

^d*P* < 0.05 for D > S or M.

^e*P* < 0.05 for D < M or S.

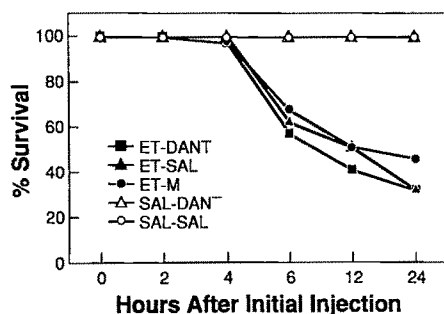


Figure 6. Percent survival over time for rats given endotoxin followed by dantrolene (ET-DANT), saline (ET-SAL), or the diluent of dantrolene (ET-M) compared with percent survival of rats given saline followed by dantrolene (SAL-DANT) or saline (SAL-SAL).

or MH (3). Dantrolene may be lifesaving in MH (1), but its effects in sepsis have not previously been studied.

Our results suggest that dantrolene is safe to administer in sepsis. Dantrolene administration to dogs in profound endotoxic shock resulted in a significant but transient improvement of the cardiac filling pressures, cardiac output, SV, LVSW, and RVSW and a decrease in the systemic and pulmonary vascular resistances. The same transient improve-

ment in cardiac performance was noted in all animals receiving the diluent solution, suggesting dantrolene itself resulted in no improvement or worsening of this artificial septic state.

Administration of dantrolene or the diluent solution resulted in a significant decrease in serum Na⁺ and total Ca compared with the control animals. Dantrolene sodium has a low solubility, requiring a large volume of diluent solution to administer the drug. The decrease in serum Na⁺ and total Ca in dogs given dantrolene or the diluent solution can be attributed to the expansion of the intravascular volume with Na⁺-poor fluid.

In contrast, the increase in serum K⁺ in dogs receiving dantrolene was not present in the diluent or septic-alone group. Significant hyperkalemia after dantrolene administration has been reported in normal dogs using pentobarbital/pancuronium anesthesia similar to our study and may be a complication of dantrolene administration peculiar to dogs (23). The hyperkalemia in normal dogs after dantrolene also has been previously associated with diminished Na⁺, Ca, and ion Ca levels compared with controls as in our study (23). We found no evidence of cardiac depression or arrhythmias from hyperkalemia, hypo-

calcemia, or hyponatremia associated with dantrolene administration.

Endotoxin administration in the rat resulted in profound shock with a 24-h mortality of 70% in this study. The addition of dantrolene or the diluent solution did not worsen the survival of the rats in septic shock. Neither the potential cardiac depression nor the depression of the contractility of the diaphragm by dantrolene was significant enough to affect survival of the rats in this model.

In summary, dantrolene administration in dog endotoxic shock resulted in a transient improvement in hemodynamics that was duplicated by the diluent solution. The improvement was accompanied, however, by hyponatremia and hypocalcemia, probably resulting from the administration of Na⁺-poor fluid. Hyperkalemia was noted after dantrolene but may be a normal canine response to dantrolene administration (23). Dantrolene did not worsen the mortality after sepsis in rats. Although humans are obviously different from the dog or rat models, the results suggest that dantrolene can be safely administered under clinical conditions where the cause of hyperthermia cannot clearly be ascribed to MH or septicemia.

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Subanesthetic Concentrations of Volatile Anesthetics May Enhance Acquired Avoidance Training in ddN Mice

Hisao Komatsu, MD, Tomoko Ohara, MD, Junko Nogaya, MD, Satoshi Yokono, MD, and Kenji Ogli, MD

Department of Anesthesiology and Emergency Medicine, Kagawa Medical School, Ikenobe, Miki-cho, Kagawa, Japan

The effects of halothane, enflurane, and isoflurane on avoidance training were assessed in male ddN mice. Animals were trained to escape an aversive unconditioned stimulus (electric foot shock) within 3 s after being exposed to a conditioned stimulus (light and buzzer). Immediately after training (first session), the animals were exposed to halothane, enflurane, or isoflurane for 120 min and were then tested again on the avoidance task (second session) 30 min after cessation of the exposure. The performance ratios [B/A] (i.e., A is the score in the first session, and B the score in the second) were compared between the anesthetic groups and their respective control groups. Performance ratios in the control animals ([B/A]c) did not reach 100% except for those corre-

sponding to the 0.5 and 1.0 MAC (minimal alveolar anesthetic concentration) halothane groups. Four of the nine performance ratios in the anesthetic groups ([B/A]a) exceeded 1.0. [B/A]a exceeded [B/A]c by 18.7% in the 0.25 MAC halothane group ($P < 0.05$), by 13.5% in the 0.31 MAC enflurane group (i.e., not significant), and by 17.3% in the 0.29 MAC isoflurane group ($P < 0.01$). [B/A]a/[B/A]c decreased dose-dependently for each anesthetic group. These results suggest that low concentrations of halothane, enflurane, and isoflurane may enhance the performance of ddN mice in acquired avoidance training performed 30 min after anesthetic exposure.

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Anesthesia is a depressive state of the central nervous system; however, during the induction of anesthesia a brief excitatory phase is often observed (1,2). In addition, transient pathological neurologic signs during emergence from anesthesia have also been reported. Soliman and Gillies (3) drew attention to the appearance of muscle spasticity in nearly all patients during recovery from general anesthesia. Rosenberg et al. (4) observed that 29 neurologically normal male patients anesthetized with halothane-nitrous oxide, enflurane-nitrous oxide, or nitrous oxide-narcotic experienced transient hyperreflexia and shivering during awakening from these anesthetics. The behavioral effects of commonly used inhaled anesthetics at subanesthetic concentrations have been described in human volunteers (5,6) and animals (7,8). The authors of these studies indicated that a variety of cognitive functions, including psychomotor ability, short-term tasks, and schedule-

controlled behaviors, are altered at subanesthetic concentrations. The authors sought to determine the effects of inhaled anesthetics on an acquired avoidance task in ddN mice at 30 min after exposure to the anesthetic.

Methods

This study was approved by the Kagawa Medical School Animal Investigation Committee. Three hundred seventy-six male ddN mice ranging in age from 8 to 12 wk were used. Their quarters were maintained at $24 \pm 1^\circ\text{C}$ with light present from 6 AM to 6 PM. They were fed a standard laboratory animal diet and tap water ad libitum until the experiment was started. Each anesthetized mouse and its corresponding control mouse were littermates. Learning was tested with a training apparatus called a jump-box (Figure 1) (9). It was made of opaque plastic board ($30 \times 30 \times 30$ cm) with an electric grid floor of 8-mm brass rods, the centers of which were 30 mm apart. An escape net, 15 cm wide, was located 10 cm above the floor and ran completely around the inside of the walls. The conditioned stimulus consisted of a plain white light from a 60-W lamp and a tone from a buzzer (75 phon). Training consisted of exposing the

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Address correspondence to Dr. Komatsu, Department of Anesthesiology and Emergency Medicine, Kagawa Medical School, 1750-1, Ikenobe, Miki-cho, Kagawa, 761-07 Japan.

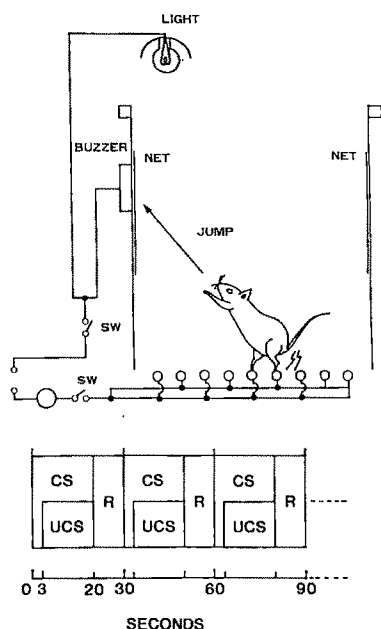


Figure 1. A schematic side view of the jump-box type avoidance training apparatus and a schedule of the training. The training consists of exposing the animal to the CS (conditioned stimulus; light and tone from a buzzer) for 3 s after which the UCS (unconditioned stimulus: the electric foot shock) is given concurrently with the CS. The shock is 40 V AC and is given for up to 17 s through the grid floor. Both stimuli are removed when the mouse makes an escape response. Each trial is completed in 30 s. If avoidance training has been established, the animal jumps up and clings to the escape net before the onset of the UCS. See text for further elaboration. R, rest.

animal to the conditioned stimulus for 3 s after which the unconditioned stimulus (UCS, the electric foot shock) was given concurrently with the conditioned stimulus. The shock was 40 V AC and was given, at most, for 17 s through the grid floor. Both stimuli were removed when the mouse made an escape response. The average time from the start of one trial to that of the next trial was 30 s. If the animal jumped up and clung to the escape net before the onset of the UCS, an avoidance response was judged to have occurred (9) and the trial was scored as 1.0 point. If jumping and the UCS occurred simultaneously, the trial was scored as 0.5 point. If the UCS occurred before the animal had clung to the net, the trial was scored zero. Each animal was given 20 training trials in 10 min (the first session), and we regarded the total points in the last 10 trials as basal points ([A]). If [A] was less than six we omitted the mouse from further study, considering avoidance learning not to be established. Seven animals were eliminated in the present study. Trials of a control mouse and its corresponding anesthetized mouse were alternated at about 10-min intervals. The anesthetic group of mice inhaled an anesthetic in a 12-L plastic chamber with a CO₂ absorber for 2 h immediately after train-

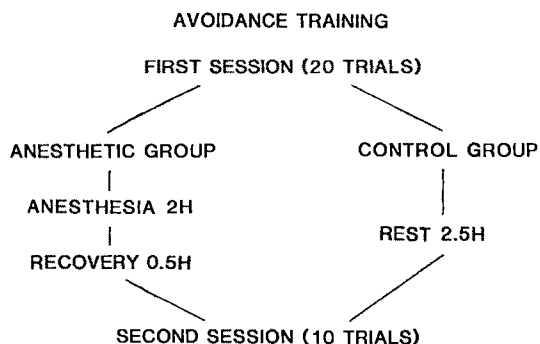


Figure 2. Experimental procedure. The control mice were treated exactly the same as the animals that were given anesthetic.

ing. This anesthetic chamber was very similar to the housing cage to reduce the effects of the environment on behavior. After 2 h of exposure to an anesthetic, the mice were transferred back to their cage and allowed to recover from anesthesia. Thirty minutes after exposure to an anesthetic, the mice were given another 10 trials of the task (the second session). After the first session, the control group of mice rested for 2 h without food or water, inhaling a 5-L/min air flow in the 12-L plastic chamber. This was similar to the anesthetic chamber with a CO₂ absorber. They were then transferred back to their housing cage and allowed to rest for 0.5 h until the second session was started. The total points in the second session were expressed as [B]. We compared the performance ratio [B/A] in the anesthetic group with that of the control group (Figure 2). All experiments were performed during the same period of day, from noon to 5 PM. The room temperature was maintained at 22 ± 2°C throughout the experiment. To enable these studies to resemble double-blind experiments, avoidance training was performed by a technician with no knowledge about the anesthetics.

Through the vaporizer, the air-anesthetic gas mixture (5 L/min) entered the 12-L chamber at the low (0.25, 0.31, or 0.29 MAC of halothane, enflurane, or isoflurane, respectively), middle (0.5, 0.61, or 0.59 MAC, respectively), or high (1.0, 1.23, or 1.18 MAC, respectively) concentration of anesthetic. Using the rolling response data reported by Ogli et al. (10), we regarded concentrations of 0.97% halothane, 1.63% enflurane, and 1.02% isoflurane as the MACs for ddN mice. Anesthetic concentration was continuously monitored using an infrared anesthetic gas analyzer (Normac). Intergroup comparisons of the performance ratio ([B/A]) were obtained by Student's *t*-test for unpaired data, with *P* < 0.05 considered significant.

Results

Observation of Anesthetic Levels in ddN Mice

In the low-concentration (0.25–0.31 MAC) groups of each anesthetic, mice increased their activity (running around and jumping in the chamber) during the initial exposure to anesthetic (0–15 min). They became sedate after this period and continued to be sedate although with frequent short bouts of walking. After the cessation of anesthetic, recovery from the sedate state was very rapid (within 10 s in most cases) and no abnormal behavior was observed when the second session was performed.

In the middle-concentration (0.5–0.61 MAC) groups, mice were much more active during the initial exposure (0–10 min) than those in the low-concentration groups. After that period, some were deeply sedated although others were not. Some of them continued moving their tails and heads. All recovered quickly and no abnormal behavior was seen at the beginning of the second session.

The high-concentration (1.0–1.23 MAC) groups of mice were rapidly anesthetized, usually within several minutes, and remained in an anesthetized state for the duration of their exposure to the anesthetic. After cessation of the anesthetic, most of the mice began to walk again within 20 min. Again, no abnormal signs were observed at the start of the second session.

Performance Ratio in the Control Group ([B/A]c)

Each [B/A]c, except for those corresponding to the 0.5 and 1.0 MAC halothane groups, was below 100% (Table 1).

Performance Ratio in the Anesthetic Group ([B/A]a)

In each concentration level of the halothane group and in the 0.29 MAC isoflurane group, [B/A]a exceeded 100%. No [B/A]a exceeded 100% in the enflurane groups. [B/A]a decreased as the concentration increased in each anesthetic group (Table 1).

Comparison of Performance Ratio in the Anesthetic Group ([B/A]a) With That of the Respective Control Group ([B/A]c)

Each [B/A]a in the low-concentration group exceeded the [B/A]c of its control group: by 18.7% in the halothane group ($P < 0.05$), by 13.5% in the enflurane group (not significant), and by 17.3% ($P < 0.01$) in the isoflurane group. The ratio of [B/A]a to [B/A]c ([B/A]a/[B/A]c) decreased with increasing anesthetic concen-

Table 1. Effects of Anesthetics on Acquired Avoidance Training

Anesthetic concentration (MAC)	[B/A]c (%)	n	[B/A]a (%)	n	[B/A]a/[B/A]c (%)
Halothane					
0.25	94.6 ± 4.0	20	106.6 ± 4.7 ^a	20	118.7 ± 6.5 ^b
0.5	102.9 ± 4.9	22	105.3 ± 5.1	22	112.1 ± 4.7
1.0	101.7 ± 2.9	35	101.1 ± 4.2	35	104.4 ± 4.7
Enflurane					
0.31	97.1 ± 4.2	18	98.3 ± 3.0	18	113.5 ± 8.4 ^b
0.61	90.5 ± 3.4	20	88.4 ± 3.1	20	101.0 ± 5.6
1.23	99.6 ± 4.0	20	84.6 ± 4.1 ^a	20	88.4 ± 6.7
Isoflurane					
0.29	91.0 ± 3.2	18	103.4 ± 3.8 ^c	18	117.3 ± 7.4 ^b
0.59	90.2 ± 4.0	20	95.0 ± 3.9	20	108.1 ± 5.6
1.18	89.0 ± 4.6	15	83.8 ± 3.5	15	98.7 ± 3.4

A, points for avoidance training in the latter half (10 trials) of the first session (20 trials); B, points for avoidance training in the second session (10 trials); [B/A]c, B/A in control group; [B/A]a, B/A in anesthetic group.

Values are mean ± SEM.

^aSignificant difference compared with control group ($P < 0.05$).

^bSignificant difference compared with high-concentration (~1 MAC) anesthetic group ($P < 0.05$).

^cSignificant difference compared with control group ($P < 0.01$).

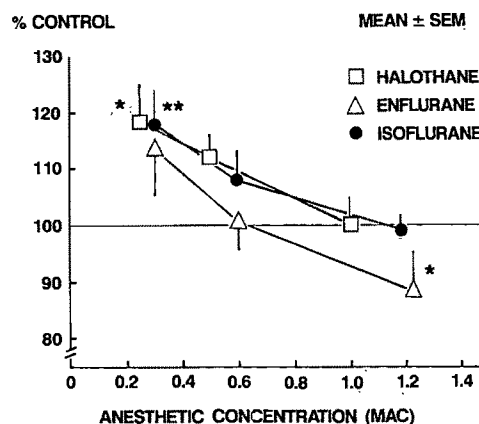


Figure 3. The comparative ratio of the performance ratios of the anesthetic group to those in the control group ([B/A]a/[B/A]c) is shown as a percentage. Note that the ratio in the low-anesthetic-concentration group obviously exceeds its control group and that the comparative ratio decreases with increasing concentration of anesthetic. *Significant difference compared with the control group ($P < 0.05$). **Significant difference compared with the control group ($P < 0.01$).

tration, and the ratio in the low-concentration group significantly exceeded that in the high-concentration group ($P < 0.05$). There were no significant differences among the MAC groups with similar concentrations of the three anesthetics (Table 1, Figure 3).

Discussion

In a study assessing the effects of anesthetics on animal behavior, the control and anesthetic animals

should be of a uniform quality and should undergo the same conditions. However, animals have cyclic biorhythms such as the circadian rhythm and the ultradian rhythm. The former has a cycle of 24 h and the latter has a shorter cycle of 60–90 min in rats (11). Therefore, we paired littermates as control and anesthetic animals and used a separate control group for each set of animals. Both the control and the anesthetic animals were given avoidance training within 12 min of each other. These considerations increased our confidence in the experimental results.

The control animals tended to do less well on their second session when compared with the latter half of their first session. This may be partly due to spontaneous memory decay during the resting time. Although the performance ratio in the control group ($[B/A]_c$) revealed some variability that may have resulted from different conditions (e.g., circadian and/or ultradian rhythms, temperatures) (Table 1), we maintained our confidence in the results by examining the control and anesthetic mice at nearly the same time.

We cannot determine the exact concentration of anesthetic in the brain during the second session. In humans, after a 30-min recovery period, the residue alveolar anesthetic concentration of halothane may be roughly estimated as about 20% of that immediately preceding recovery from 2 h of inhalation, and this is likely to be reflected in the brain to some extent (12). The concentrations of enflurane and isoflurane are likely to be less than 20% because their solubilities are smaller than that of halothane under controlled ventilation (12). Recently, Litt et al. (13) reported that in living rats, after the 60-min inspired halothane concentration decreased to zero, the nuclear magnetic resonance signal (halothane concentration) decreased to 40% of its maximum value within 34 ± 8 min. An in vivo fluorine nuclear magnetic resonance study of isoflurane revealed a rapid decrease in the brain anesthetic signal to approximately 50% during the first 30 min after cessation of exposure in rabbits (14).

Our results suggest that in ddN mice, 2-h exposure to low concentrations of anesthetic immediately after training improved the acquired avoidance training score performed 30 min after the anesthetic exposure. The improvement in training scores was about 1.19 times, 1.14 times, and 1.17 times that of the control groups for the low-concentration groups of halothane, enflurane, and isoflurane, respectively. Wenger and Dews (8) studied the response of mice to the breaking of a light beam focused on a photocell that was programmed to produce food according to a multiple schedule with alternating 30-response fixed ratio, 300-s fixed interval (FR-30, FI-300 s) components (8). The first pattern, FR-30, requires 30 break-

ings of the light beam in succession to receive food. The second pattern, FI-300 s, is known as the pattern where the first beam break after a 300-s elapsed interval is reinforced with a reward of food. They found that the four agents (pentobarbital, *d*-amphetamine, phencyclidine, and ketamine) produced an increase in the fixed interval response rate and that the maximum increases in the fixed interval average rates were 1.83, 1.25, and 1.32 times the control rate for *d*-amphetamine (1 mg/kg), ketamine (100 mg/kg), and phencyclidine (3 mg/kg), respectively. Pentobarbital increased both the fixed ratio and fixed interval response rate to 1.25 times the control rate at a dose of 3 mg/kg. Garfield and Vivaldi (7) reported that a FI-5 min component in schedule-controlled behavior in rats showed no significant effect with halothane ($<0.23\%$) or enflurane ($<0.278\%$); however, they also indicated an increased tendency in responses at concentrations of 0.115% halothane or 0.116% and 0.175% enflurane. In a human study, a concentration of 50 ppm nitrous oxide + 1.00 ppm halothane improved a vigilance response (6). (The subject recognizes a brief [1–2 s] change to a pattern of atrial fibrillation that is interposed among the normal electrocardiographic patterns.) Although Cook et al. could not confirm this report (5), these results seem to coincide with our data. Behavioral responses in these studies seem to be enhanced by low concentrations of anesthetics. Some drugs that stimulate the central nervous system facilitate learning and memory (15). Moreover, our results suggest the possibility of enhancing memory retention by the administration of low concentrations of volatile anesthetics, given that diazepam induces a retrograde memory facilitation produced by interference reduction (16). We also cannot deny the possibility that introducing experimental animals to a new environment (inhaling an aversive smelling gas) might have had a stimulating effect, leading to enhanced performance.

The comparative ratio of performance ratios in the anesthetic group to those in the control group ($[B/A]_a/[B/A]_c$) decreased as the inspired anesthetic concentration increased. We supposed that this might be due to the residual sedative effect of higher anesthetic concentrations or be due to a presumed depressive effect on memory consolidation and/or retention and/or recall. Although, in our present study, we did not determine the recovery time of each animal from anesthesia, our preliminary study indicated that the order of the recovery time required to begin to walk was as follows: isoflurane < enflurane < halothane. Isoflurane-anesthetized mice emerged more rapidly than the halothane-anesthetized mice. Nevertheless, the former appeared to perform less well. This may partly be caused by the inhaling of relatively higher concentra-

tions of isoflurane than halothane and by the greater residual analgesic action of isoflurane than that of halothane (17). Isoflurane may mitigate the pain from the electric foot shock and thus reduce the improvement in the avoidance training. Additionally, enflurane-anesthetized mice tended to perform poorly compared with isoflurane- or halothane-anesthetized mice. This also may be explained by the high analgesic potency of enflurane (17).

In summary, 2 h of exposure to low concentrations of halothane, enflurane, and isoflurane immediately after training may enhance acquired avoidance training performed after a 30-min recovery period. This may result from a central nervous system-stimulating effect of low concentrations of volatile anesthetics.

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Sweating Threshold During Isoflurane Anesthesia in Humans

Daniel I. Sessler, MD

Department of Anesthesia, University of California, San Francisco, California

Isoflurane anesthesia in humans markedly decreases the threshold temperature triggering peripheral thermoregulatory vasoconstriction (i.e., central temperature triggering vasoconstriction). However, it is not known whether the sweating threshold remains unchanged (e.g., near 37°C), decreases along with the vasoconstriction threshold, or increases during anesthetic administration. Accordingly, the hypothesis that isoflurane anesthesia increases the thermoregulatory threshold for sweating was tested. Forehead sweating was evaluated in five healthy patients given

isoflurane anesthesia. The sweating threshold was prospectively defined as the distal esophageal temperature at which significant sweating was first observed. Sweating was observed in each patient at a mean central temperature of $38.3 \pm 0.3^\circ\text{C}$ and an end-tidal isoflurane concentration of $1.1\% \pm 0.2\%$. The interthreshold range (difference between vasoconstriction and sweating thresholds) without anesthesia is $\sim 0.5^\circ\text{C}$; isoflurane anesthesia increases this range to $\sim 4^\circ\text{C}$.

(Anesth Analg 1991;73:300-3)

Regulatory responses to hypothermia and hyperthermia can be defined in terms of *thresholds* (central temperatures triggering protective actions) (1). In anesthetized, paralyzed patients, only cutaneous vasoconstriction and nonshivering thermogenesis are available defenses against hypothermia. Halothane (2), isoflurane (3-5), and fentanyl-nitrous oxide (6) anesthesia inhibit central thermoregulatory peripheral cutaneous vasoconstriction. Although nonshivering thermogenesis is an important source of metabolic heat in anesthetized infants (Bissonnette B, Sessler DI, unpublished data), oxygen consumption does not increase in hypothermic adults (7).

Anesthetized patients may respond to hyperthermia with active vasodilation and sweating. From the vasoconstriction data, it was not possible to determine whether the sweating threshold remained unchanged (e.g., near 37°C), decreased along with the vasoconstriction threshold, or increased during anesthetic administration. However, sweating is rarely observed at the normal or hypothermic central temperatures typical during surgery. Therefore, the hypothesis that the thermoregulatory threshold for

sweating is elevated by isoflurane anesthesia was tested.

Methods

With approval from the Committee on Human Research of the University of California, San Francisco, the sweating threshold was measured in five ASA physical status I patients scheduled for peripheral microvascular surgery. None was obese, was taking medication, or had a history of thyroid disease, dysautonomia, Raynaud's syndrome, or malignant hyperthermia.

Without any preanesthetic medication, anesthesia was induced using 4-5 mg/kg of thiopental and up to 500 μg of fentanyl. Rapid-sequence tracheal intubation with cricoid pressure was facilitated by intravenous administration of 100 mg of succinylcholine. Anesthesia was maintained with isoflurane (1%-1.4% end-tidal concentration) in oxygen, and the patients' lungs were mechanically ventilated to maintain end-tidal CO_2 at 35-40 mm Hg.

Respiratory gases were administered via a partially rebreathing circle system. Gas concentrations were quantified using a mass spectrometer (Medspect, St. Louis, Mo.) or a Datex Capnomac end-tidal gas analyzer (Datex Medical Instrumentation, Tewksbury, Mass.). The Capnomac analyzer was calibrated using a known mixture of gases before each study. Airway humidification was provided by placing a

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Address correspondence to Dr. Sessler, Department of Anesthesia, Room C-214, University of California, San Francisco, CA 94143-0548.

heat and moisture exchanger between the Y-piece of the circle system and the endotracheal tube. Approximately 1 L of room-temperature lactated Ringer's solution was administered during each anesthetic study. Isoflurane and fluid administration were adjusted to maintain systolic arterial blood pressure near 100 mm Hg.

To increase peripheral blood flow and to facilitate microvascular repairs, the surgeons in each case requested that central temperature be increased to 38°–39°C. A full-length Bair Hugger cover (Augustine Medical, Eden Prairie, Minn.) was placed directly over each patient, then covered with a cotton blanket. The cover was inflated using a model 200 Bair Hugger warmer set on "high." We have previously demonstrated that this system transfers ~50 W across the skin surface and will raise mean body temperature ~1.5°C/h (8). The patient's entire head remained exposed to the ambient environment, which was maintained near 23°C.

Central temperature was measured in the esophagus using Mon-a-Therm model 6500 thermometers (St. Louis, Mo.); the thermocouple probe was incorporated into a disposable esophageal stethoscope and positioned at the distal end of the range of maximal heart sounds. Distal esophageal temperature correlates well with tympanic membrane temperature (9).

At 10-min intervals (starting after induction of anesthesia), forehead sweating was qualitatively evaluated: a sweating grade of 0 was assigned when no moisture could be detected, a grade of 1 when some moisture was detected, and a grade of 2 when distinct beads of sweat were visible. The forehead was swabbed dry using a gauze pad immediately after each sweating evaluation. Sweating was evaluated on the exposed forehead because sweating intensity may be increased slightly by local cutaneous warming (10,11).

Grade 2 sweating was prospectively defined as significant, and the central temperature at which significant sweating was detected was considered the thermoregulatory threshold for sweating. All data are presented as mean \pm standard deviations.

Results

The mean age of patients was 46 ± 15 yr, and weight 74 ± 11 kg. During induction of anesthesia, patients were given 338 ± 138 mg (range, 200–500) of sodium thiopental and 163 ± 236 μ g (range, 0–500) of fentanyl.

Grade 2 sweating was observed in each patient 235 ± 126 min (range, 120–430) after induction of anesthesia at a central temperature of $38.3 \pm 0.3^\circ\text{C}$ (range, 38.0–38.7). At that time, the end-tidal isoflurane concentration was $1.1\% \pm 0.2\%$ (range, 1.0–1.4)

and the end-tidal CO_2 partial pressure was 37 ± 2 mm Hg.

Discussion

Thermoregulatory responses can be modeled using the engineering terms *threshold* and *gain*. The threshold for a particular regulatory effector is defined as the central temperature triggering that response. Gain quantifies the intensity of the response as central temperature further deviates from the triggering threshold (1). The difference between the temperatures triggering responses to hypothermia (e.g., vasoconstriction, shivering) and hyperthermia (e.g., active vasodilation, sweating) is called the *interthreshold range*. Temperature changes within the interthreshold range are probably easily detected by the thermoregulatory system (12) but do not provoke physiologic responses. In normal, unanesthetized individuals, this range is only $\sim 0.5^\circ\text{C}$ (13).

The patients in this study started to sweat at a central temperature of $38.3 \pm 0.3^\circ\text{C}$ while receiving $1.1\% \pm 0.2\%$ isoflurane. This increase in the sweating threshold was caused by an isoflurane concentration known to decrease the threshold triggering vasoconstriction by $\sim 3.3^\circ\text{C}$ (3). Thus, the interthreshold range increased from $\sim 0.5^\circ\text{C}$ to $\sim 4^\circ\text{C}$. Within this range, anesthetized patients will be poikilothermic; their central temperatures will vary as a result of redistribution of heat within the body and alterations in metabolic heat production and heat loss to the environment. However, thermoregulatory responses during 1.1% isoflurane anesthesia will occur at central temperatures above $38.3 \pm 0.3^\circ\text{C}$ or below $\sim 33.7^\circ\text{C}$.

Isoflurane anesthesia caused a considerably smaller increase in the sweating threshold than decrease in the threshold for vasoconstriction ($-3.1^\circ\text{C}/\%$ isoflurane) (3). Teleologically, an aggressive sweating response is appropriate because hyperthermia is more dangerous than comparable hypothermia. Similar asymmetrical widening of the interthreshold range is typical in animals given chloralose-urethane, ethanol, pentobarbital, and morphine (14–20). Sweating was commonly observed during hyperthermic surgery (in tropical environments, before air-conditioning was available) and usually limited central temperatures to $\leq 39^\circ\text{C}$ (21).

Isoflurane anesthesia does not impair the intensity of thermoregulatory vasoconstriction (once triggered) (3,5). Although this study did not quantify intensity (i.e., gain) of the sweating response, the intensity was high and the onset easily detected. Despite being covered by a warmer transferring ~ 50 W across the skin via convection and radiation (8), the patients' central temperatures either remained constant or

decreased after sweating started. Effective hyperthermia prevention is consistent with the observation that well-hydrated, unanesthetized humans in a dry, convective environment can lose five times their basal metabolic rates by sweating (13). (Shivering, in contrast, usually only doubles basal heat production [22,23].) It is such evaporative heat loss that allows humans to live safely at ambient temperatures exceeding 37°C.

Sweating during anesthesia can indicate inadequate anesthetic depth. However, the patients participating in this study appeared well-anesthetized (using blood pressure, heart rate, and absence of movement as criteria). The MAC of isoflurane increases only ~5%/°C central body temperature (24); it is therefore unlikely that sweating resulted from inadequate anesthesia. Thiopental and fentanyl are short-acting drugs and probably did not significantly increase the sweating threshold more than 2 h after they were administered. None of the drugs used in these patients is likely to directly inhibit the postganglionic, cholinergic, sympathetic nerves that mediate thermoregulatory eccrine sweating (25).

All the patients in this study were young and relatively healthy; it is likely that sweating thresholds differ at the extremes of age and in patients with severe systemic illness. Sweat production is normally a function of both central and skin-surface temperature (10,11,26). The threshold during isoflurane anesthesia may, therefore, be higher when skin temperature remains relatively low. However, we have previously demonstrated that the sweating threshold also is ~38°C during rewarming by cardiopulmonary bypass in patients given high-dose opioids (27).

In summary, isoflurane anesthesia in humans markedly decreases the threshold temperature triggering peripheral thermoregulatory vasoconstriction (i.e., central temperature triggering vasoconstriction). However, it is not known whether the sweating threshold remains unchanged (e.g., near 37°C), decreases along with the vasoconstriction threshold, or increases during anesthetic administration. Accordingly, the author tested the hypothesis that isoflurane anesthesia increases the thermoregulatory threshold for sweating. Forehead sweating was evaluated in five healthy patients given isoflurane anesthesia. The sweating threshold was prospectively defined as the distal esophageal temperature at which significant sweating was first observed. Sweating was observed in each patient at a mean central temperature of $38.3 \pm 0.3^\circ\text{C}$ and an end-tidal isoflurane concentration of $1.1\% \pm 0.2\%$. The interthreshold range (difference between vasoconstriction and sweating thresholds) without anesthesia is ~0.5°C; isoflurane anesthesia increases this range to ~4°C.

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Effects of Volatile Anesthetics on Response to Norepinephrine and Acetylcholine in Guinea Pig Atria

Astride B. Seifen, MD, Richard H. Kennedy, PhD, and Ernst Seifen, MD, PhD

Departments of Pharmacology and Toxicology, and Anesthesiology, University of Arkansas for Medical Sciences, Little Rock, Arkansas

The in vitro chronotropic and inotropic effects of norepinephrine and acetylcholine in isolated right and left guinea pig atria were examined in the absence and presence of halothane, isoflurane, and enflurane (0.6 and 1.2 MAC). All three anesthetics elicited dose-dependent reductions in contractile force and spontaneous pacemaker activity. The maximal developed tension observed in the presence of norepinephrine was not altered by the anesthetics and corresponding ED₅₀ values increased only in the presence of 1.2 MAC halothane and 1.2 MAC isoflurane. The anesthetics did not affect (a) the maximal positive chronotropic effect of norepinephrine, (b) the ED₅₀ values for its positive chronotropic effect, and

(c) acetylcholine-induced negative inotropic and chronotropic actions and did not induce arrhythmic activity even in the presence of the maximally effective neurotransmitter concentrations. These findings indicate that in isolated guinea pig atria volatile anesthetics, in concentrations up to 1.2 MAC, do not alter the inotropic and chronotropic effects of norepinephrine or acetylcholine and do not induce arrhythmogenic action in the presence of the neurotransmitters. These data suggest that altered atrial responsiveness to adrenergic or muscarinic stimulation does not contribute to the development of anesthetic-induced cardiac arrhythmias.

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Many volatile anesthetics promote arrhythmias induced by sympathomimetic drugs. This event, often termed "myocardial sensitization" to catecholamines (1), can be elicited in humans and intact animals (2-7) by anesthetics that are not considered to be arrhythmogenic by themselves. A study in humans indicates that the arrhythmogenic effect of catecholamines is increased most by halothane, less by isoflurane, and least by enflurane (2). In contrast to this well-documented sensitization observed in vivo, an anesthetic-induced enhancement of responsiveness to catecholamines has not been clearly demonstrated in isolated myocardial preparations (8). Does this myocardial sensitization actually occur in the heart, or is it possibly mediated by extracardiac actions of the anesthetics such as effects on the sympathetic nervous system? Further-

more, recent data indicate that an increase in vagal tone protects against catecholamine-halothane-induced ventricular fibrillations in dogs (9), and that volatile anesthetics affect muscarinic receptor/G-protein coupling (10). This information suggests that the interaction of these anesthetics with cholinergic stimulation of the heart also needs to be considered as a possible mechanism of myocardial sensitization to catecholamines.

The present study was undertaken to examine the effects of the three most commonly used volatile anesthetics on (a) dose-dependent actions of norepinephrine and acetylcholine and (b) the occurrence of arrhythmias in atrial preparations isolated from guinea pig hearts in vitro. Experiments established dose-response curves for inotropic and chronotropic effects of the two neurotransmitters in the absence and presence of 0.6 and 1.2 MAC halothane, isoflurane, or enflurane.

Methods

After approval of this study had been received from the institutional animal care and use committee, male Hartley guinea pigs (250-300 g) were killed and their hearts were excised and immediately perfused from the aorta with Krebs-Henseleit solution containing

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Address correspondence to Dr. E. Seifen, Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, 4301 West Markham Street, Little Rock, AR 72205.

119 mM NaCl, 25.0 mM NaHCO₃, 4.7 mM KCl, 1.2 mM MgCl₂, 1.8 mM CaCl₂, and 11.1 mM glucose. This solution was maintained at 37°C and saturated with 95% O₂/5% CO₂, resulting in a pH of 7.4. After all detectable blood was washed from the heart, left and right atria were dissected from the heart and suspended separately in water-jacketed muscle baths (37°C) containing the Krebs-Henseleit solution described. Left atria ($n = 36$) were used to measure force of isometric contraction; they were maintained at a resting tension (preload) of 1.0 g (resulting in ~95% of the force developed at optimal preload) and paced at 3.3 Hz by 0.2-ms square-wave pulses set 50% above threshold voltage. Right atria ($n = 36$) were used to measure sinoatrial-nodal pacemaker activity; the rate of spontaneous (nonpaced) contractions was monitored by means of a tachograph using signals from force-displacement transducers (preload 0.5 g). All signals were continuously recorded on a polygraph (model 7-D; Grass, Quincy, Mass.), which allowed observation of possible occurrence of arrhythmias. A stabilization period of 60 min was allowed before atria were challenged by various agents. During this equilibration period, the bathing solution was exchanged at 15-min intervals. In experiments using acetylcholine, nadolol (1×10^{-7} M), a β -adrenergic antagonist, was added to the physiologic salt solution to minimize effects of catecholamines possibly released from the tissue (11). Ethylenediamine tetraacetic acid (1×10^{-5} M) was added in all experiments to minimize neurotransmitter degradation (12). In the concentrations used, neither nadolol nor ethylenediamine tetraacetic acid changed spontaneous rate or force development of the isolated guinea pig atria.

Left and right atria were used to monitor the effects of volatile anesthetics on the inotropic and chronotropic actions of norepinephrine and acetylcholine. The effects of the two neurotransmitters were examined separately, in six left and six right atria each, in the absence and presence of two concentrations of a single anesthetic. When using norepinephrine, atria were first exposed for 4 min to a single (desensitizing) concentration of the agonist (1×10^{-5} M); norepinephrine was removed from the tissue bath by repeated washings, and 30 min later, when developed tension and spontaneous rate had returned to control values, cumulative dose-response curves were obtained; each succeeding dose of norepinephrine was added only after preparations had reached a steady-state response to the preceding concentration. After completion of dose-response curves, norepinephrine was washed from the tissue bath. Next, one of the volatile anesthetics (halothane, enflurane, or isoflurane) was admixed (using standard anesthetic vaporizers; Ohio Medical Products,

Madison, Wis.) to the O₂/CO₂ gas mixture saturating the physiologic salt solution. Anesthetic concentrations of the gas mixture delivered to, and in the gas phase immediately above the bath solution, were continuously measured with an anesthetic agent monitor (AAM 222; Puritan-Bennett, Wilmington, Mass.) that was calibrated daily with calibration gases of the chosen anesthetic (Scott Medical Products, Plumsteadville, Pa.). Atrial preparations were exposed for 30 min in random order to each of two anesthetic concentrations (0.6 and 1.2 MAC for guinea pigs [13]) before baseline values were recorded and norepinephrine dose-response curves were established. Preparations were then allowed to recover from the anesthetic (30–35 min), and a final norepinephrine dose-response curve was obtained. There were no significant differences between dose-response curves obtained before (controls) and after (recovery) exposure to the volatile agents. A similar protocol was used to establish cumulative acetylcholine dose-response curves with the exception that previous exposure to a single large (desensitizing) dose was not needed to obtain consistent control and recovery dose-response curves for this agent.

Acetylcholine chloride and *d,l*-norepinephrine hydrochloride were purchased from Sigma Chemical Co. (St. Louis, Mo.). Halothane was purchased from Halocarbon Laboratories (Hackensack, N.J.), and enflurane and isoflurane were obtained from Anaquest (Madison, Wis.). All other chemicals were reagent grade. Fresh stock solutions of norepinephrine and acetylcholine were prepared daily using 0.01 N HCl as diluent. Administration of diluent alone (vehicle controls) did not change the pH of the tissue bath solution nor did it elicit any noticeable effect on left atrial force development or right atrial spontaneous rate.

Data were statistically evaluated by analysis of variance with individual mean values being compared by Duncan's multiple range test. *P*-values smaller than 0.05 were the criterion for significance. Data are presented as mean \pm SEM. ED₅₀ values for norepinephrine and acetylcholine were obtained graphically for each individual experiment.

Results

Figure 1 shows the effects of halothane, isoflurane, and enflurane on the positive inotropic action of norepinephrine in isometrically contracting guinea pig left atria paced at 3.3 Hz. All three anesthetics elicited dose-dependent reductions in developed tension as reported previously (14). However, they had little effect on the action of norepinephrine. Maximal contractile force observed in the presence of norepinephrine was not altered by the anesthetics. The

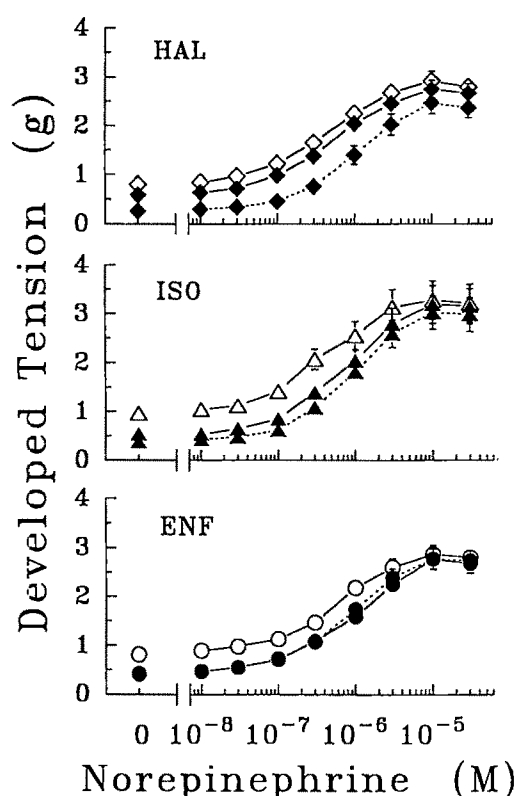


Figure 1. Effects of halothane (HAL), isoflurane (ISO), and enflurane (ENF) on the positive inotropic action of norepinephrine in isometrically contracting guinea pig left atria ($n = 6$ for each anesthetic). Preparations were suspended in Krebs-Henseleit buffer (37°C) and paced at 3.3 Hz. Dose-response curves were obtained by cumulative addition of norepinephrine before (open symbols) and after a steady-state response to each level of anesthetic had been established (filled symbols: solid lines represent 0.6 and dashed lines 1.2 MAC, respectively). Symbols indicate means and vertical bars indicate SEM (not visible when smaller than symbols).

norepinephrine dose-response curves tended to shift rightward, and corresponding ED_{50} values increased (Table 1); however, these changes reached statistical significance only with 1.2 MAC halothane and isoflurane.

Interactions between volatile anesthetics and the chronotropic effects of norepinephrine are shown in Figure 2. Halothane (top panel), isoflurane (middle), and enflurane (bottom) reduced spontaneous right atrial pacemaker rate in the absence and in the presence of norepinephrine. ED_{50} values for the positive chronotropic effect of norepinephrine were not affected (Table 1).

The negative inotropic effects of acetylcholine in left atrial muscle were also compared in the presence and absence of the three anesthetics (Figure 3). Acetylcholine-induced changes in contractile force were not significantly altered by any of the volatile agents, as indicated by the absence of a shift in the dose-response curves as well as the lack of significant

Table 1. ED_{50} Values for Norepinephrine and Acetylcholine Obtained in Guinea Pig Left Atrial and Right Atrial Muscle Preparations Suspended in Krebs-Henseleit Buffer (pH 7.4 at 37°C)

Anesthetic	$\text{ED}_{50} (\times 10^{-7} \text{ M})$			
	NE		ACh	
	LA	RA	LA	RA
Halothane				
0.0 MAC	5.0 ± 0.4	6.1 ± 1.1	2.5 ± 0.7	4.7 ± 1.0
0.6 MAC	5.2 ± 0.5	7.2 ± 1.5	1.9 ± 0.4	4.0 ± 1.2
1.2 MAC	11.3 ± 1.6^a	8.8 ± 1.3	2.2 ± 0.4	4.4 ± 1.1
Isoflurane				
0.0 MAC	6.6 ± 0.7	4.3 ± 0.6	5.2 ± 1.1	5.9 ± 2.5
0.6 MAC	7.7 ± 0.5	3.7 ± 0.5	6.3 ± 1.7	4.5 ± 1.3
1.2 MAC	8.4 ± 0.7^a	4.1 ± 0.5	7.6 ± 1.3	6.3 ± 2.2
Enflurane				
0.0 MAC	6.1 ± 1.2	4.9 ± 0.5	7.8 ± 1.2	4.9 ± 1.7
0.6 MAC	9.5 ± 2.1	6.4 ± 1.2	6.0 ± 0.7	3.7 ± 1.4
1.2 MAC	7.6 ± 1.5	5.8 ± 0.8	6.2 ± 1.3	4.8 ± 1.3

MAC, minimum alveolar anesthetic concentration; NE, norepinephrine; ACh, acetylcholine; LA, left atria; RA, right atria.

Left atria were contracting isometrically at 3.3 Hz, and right atria were beating spontaneously. Anesthetic levels are given in MAC values for guinea pigs. Values are mean \pm SEM ($n = 6$ each).

^aSignificantly different ($P < 0.05$) from values observed at 0 MAC.

changes in ED_{50} values (Table 1). Similarly, the negative chronotropic actions of acetylcholine remained unchanged in the presence of the three anesthetics (Figure 4 and Table 1).

In none of the guinea pig left or right atrial preparations were arrhythmias observed before, during, or after exposure to any of the anesthetics. Furthermore, neither in the absence nor in the presence of these anesthetics was arrhythmic activity observed in any of the atria when norepinephrine or acetylcholine dose-response curves were established.

Discussion

Volatile anesthetics such as halothane, enflurane, and isoflurane are generally not considered to possess appreciable arrhythmogenic properties (15). However, "sensitization" of the myocardium to catecholamine-induced arrhythmias has been quantified in animals (5-7,16-18) as well as in humans (2-4). Many of these studies in intact organisms indicate that arrhythmogenic doses of epinephrine are significantly reduced in the presence of anesthetics. In isolated cardiac preparations, however, myocardial sensitization by hydrocarbon anesthetics has not been clearly demonstrated. Flacke and Alper (8) studied chronotropic actions of norepinephrine in the dog heart-lung preparation. They found no significant differences in the positive chronotropic responses to norepinephrine in the presence or absence of

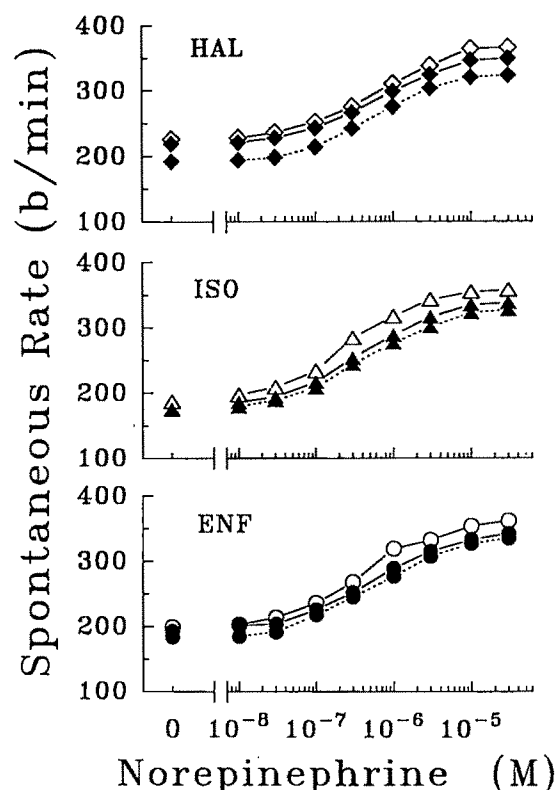


Figure 2. Effects of halothane (HAL), isoflurane (ISO), and enflurane (ENF) on the positive chronotropic action of norepinephrine in guinea pig right atria ($n = 6$ for each anesthetic). Preparations were suspended in Krebs-Henseleit buffer (37°C). Dose-response curves were obtained by cumulative addition of norepinephrine before (*open symbols*) and after a steady-state response to each level of anesthetic had been established (*filled symbols*: solid lines represent 0.6 and dashed lines 1.2 MAC, respectively). Symbols indicate means and vertical bars indicate SEM (not visible when smaller than symbols).

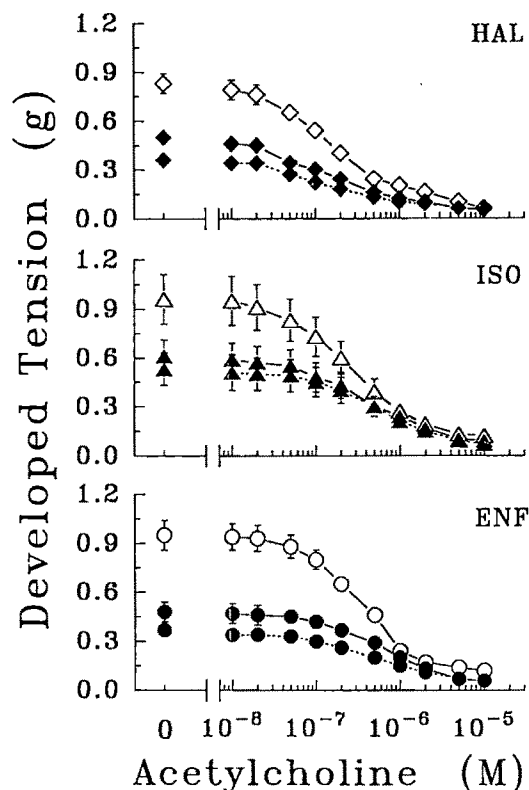


Figure 3. Effects of halothane (HAL), isoflurane (ISO), and enflurane (ENF) on the negative inotropic action of acetylcholine in isometrically contracting guinea pig left atria ($n = 6$ for each anesthetic). Preparations were suspended in Krebs-Henseleit buffer (37°C) and paced at 3.3 Hz. Dose-response curves were obtained by cumulative addition of acetylcholine before (*open symbols*) and after a steady-state response to each level of anesthetic had been established (*filled symbols*: solid lines represent 0.6 and dashed lines 1.2 MAC, respectively). Symbols indicate means and vertical bars indicate SEM (not visible when smaller than symbols).

halothane and reported that no arrhythmias were observed. Stowe et al. (19), on the other hand, found that halothane reduced by a factor of 20 the dose of epinephrine necessary to induce a 50% incidence of arrhythmic events in isolated perfused guinea pig hearts. Reynolds and coworkers (17,18) performed a multilevel study using intact animals, isolated hearts, and Purkinje fibers. In isolated canine Purkinje fibers (17), they found that halothane-induced slowing of impulse conduction was significantly more pronounced in the presence of epinephrine. In isolated cat Langendorff heart preparations perfused with halothane and epinephrine (18), ventricular arrhythmias were observed only when the afterload was raised to levels that markedly elevated left intraventricular pressure. The investigators interpreted these observations as an indication that ectopic foci were induced secondary to stretch of latent pacemaker fibers, thus demonstrating the importance of intraventricular pressure as an arrhythmogenic factor. In

intact dogs that were given epinephrine infusions either before or after induction of halothane anesthesia, the combination of halothane with epinephrine lead to the loss of sinus node dominance and an associated shift of pacemaker activity to the atrioventricular junctional area (18). The investigators attributed this finding to differential effects of the halothane-epinephrine combination on sinoatrial-nodal versus atrioventricular junctional fibers. A unique and interesting experimental design by Hashimoto et al. (20) combined the intact animal (dog) and isolated cardiac preparations (canine papillary muscle and sinoatrial node) in one simultaneous perfusion circuit. In this experimental setting, halothane sensitized the ventricle of the donor dog to the arrhythmogenic effects of norepinephrine (producing ventricular arrhythmias and sometimes ventricular fibrillation) while having no effect on responses to norepinephrine in the isolated cardiac preparations.

Information concerning the mechanisms by which

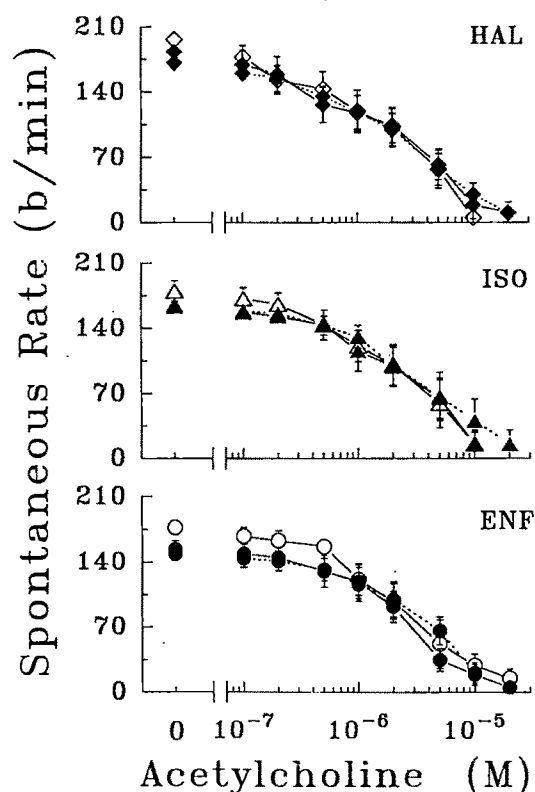


Figure 4. Effects of halothane (HAL), isoflurane (ISO), and enflurane (ENF) on the negative chronotropic action of acetylcholine in guinea pig left atria ($n = 6$ for each anesthetic). Preparations were suspended in Krebs-Henseleit buffer (37°C). Dose-response curves were obtained by cumulative addition of acetylcholine before (open symbols) and after a steady-state response to each level of anesthetic had been established (filled symbols: solid lines represent 0.6 and dashed lines 1.2 MAC, respectively). Symbols indicate means and vertical bars indicate SEM (not visible when smaller than symbols).

volatile anesthetics affect autonomic nervous system activity is limited (3,21). Reports on volatile anesthetic-induced changes in circulating plasma catecholamine levels are contradictory (15); norepinephrine levels have been reported to increase (22,23), remain unchanged (24), or decrease (25). Catecholamines exert most of their cardiac effects by stimulating β_1 -adrenoceptors, thus elevating intracellular cyclic adenosine monophosphate levels (among other changes) and increasing calcium channel activation which enhances the slow inward calcium current and increases sarcoplasmic reticular calcium uptake (26). Even though there is little evidence supporting a direct link between cellular β -adrenergic mechanisms and anesthetic-induced myocardial sensitization to catecholamines, there is apparently a close correlation between arrhythmogenic doses of epinephrine and α -adrenoceptor stimulation in intact animals (16,27).

The possible role of acetylcholine in anesthetic-induced arrhythmogenic action has been minimally

examined. One of the major effects of acetylcholine is to increase membranal potassium conductance via muscarinic receptor stimulation (28). This increase in membranal potassium conductance may cause hyperpolarization of myocardial cells and contribute to a reduced spontaneous pacemaker frequency by lowering the phase 4 slope of the action potential of sinoatrial pacemaker cells. Acetylcholine also shortens the effective refractory period of atrial muscle fibers (29) and slows impulse conduction in the atrioventricular node, probably by reducing slow inward calcium current (26). These effects of acetylcholine could promote the occurrence of various cardiac arrhythmias. Muscarinic stimulation can also antagonize myocardial actions of β -adrenergic agonists by diminishing stimulated adenylate cyclase activity (30). Radioligand binding studies in rat brainstem suggest that volatile anesthetics interfere with muscarinic receptor/G-protein coupling (10). Furthermore, halothane affects cholinergic tone by depressing synaptic transmission at multiple sites, including possible effects on presynaptic acetylcholine release or the sensitivity of postsynaptic muscarinic receptors to acetylcholine (31). Alterations in parasympathetic cardiac stimulation or responsiveness may change the arrhythmogenic effect of sympathetic stimulation. In fact, work by Waxman et al. (9) demonstrates that catecholamine/halothane-induced ventricular fibrillation is antagonized by vagal stimulation. The present study indicates that in isolated atria none of the three volatile anesthetic agents has an appreciable influence on postsynaptic or cellular cholinergic actions, thus suggesting that direct myocardial responsiveness to cholinergic action is probably not involved in the anesthetic-induced alteration of catecholamine effects observed in the intact organism. These data do not, however, rule out changes in vagal nerve activity.

Even though significant discrepancies exist in the outcome of the various investigations described (which may, at least in part, be attributable to species differences), the majority of the data appears to indicate that the cardiac sensitization to catecholamines observed in vivo is difficult to reproduce in isolated myocardial preparations. Similarly, the results of the current study show that in clinically relevant concentrations (0.6 and 1.2 MAC) none of the three commonly used volatile hydrocarbon anesthetics (halothane, isoflurane, and enflurane) altered the direct responses of guinea pig atria to norepinephrine or acetylcholine, nor did any of these anesthetics induce arrhythmogenic activity even in the presence of neurotransmitter concentrations that elicited maximal inotropic or chronotropic responses in vitro. These findings support the contention that alterations in cardiac muscle responsiveness to direct

adrenergic or cholinergic stimulation are unlikely to contribute significantly to the increased cardiac susceptibility to arrhythmias observed in the presence of anesthetics *in vivo*. The current results do not rule out, however, the possibility that (a) direct effects of the anesthetics on specialized tissues, such as the atrioventricular node or the His-Purkinje system, may predispose the heart to arrhythmogenic actions, elicited by adrenergic or cholinergic stimulation, and that (b) volatile anesthetics may interact *in vivo* with extracardiac factors that promote autonomic nervous system effects on the heart or enhance the arrhythmogenic potential of existing adrenergic and/or vagal tone.

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Age Affects the Pharmacokinetics of Inhaled Anesthetics in Humans

David P. Strum, MD, Edmond I. Eger II, MD, Jashvant D. Unadkat, PhD,
Brynte H. Johnson, MS, and Randall L. Carpenter, MD

Department of Anesthesiology, University of Pittsburgh, Pittsburgh, Pennsylvania; Department of Anesthesia, University of California, San Francisco, California; Department of Pharmaceutics, University of Washington, Seattle, Washington; Department of Anesthesia, Virginia Mason Medical Center, Seattle, Washington

To define the effect of aging on the pharmacokinetics of volatile anesthetics, we determined the end-tidal and mixed expired anesthetic concentrations of isoflurane, enflurane, halothane, and methoxyflurane during 30 min of simultaneous administration and for 5–12 days of elimination in seven healthy young patients (31 ± 1.8 yr [mean \pm SEM]) and in 11 healthy aged patients (73.2 ± 3.1 yr [mean \pm SEM]). A five-compartment mammillary function was fit to the end-tidal and mixed expired anesthetic elimination data simultaneously using ordinary least-squares analysis. We assumed the compartments to represent the following tissue groups: lungs and pulmonary capillary blood (V_1), vessel-rich tissues (i.e., liver, heart, kidneys, and brain) muscle, an unidentified fourth compartment, perhaps fat adjacent to well-

perfused tissues, and fat tissues. The tissue volumes and perfusions estimated for these compartments approximated values from the literature. In general, the volume of the fourth and fifth compartments increased with age, and perfusion to the second and fifth compartments decreased with age. Aging delayed anesthetic elimination and increased the apparent volume of distribution at steady state. These observations are compatible with decreased tissue perfusion and an increase in the ratio of fat/lean body weight in the elderly. Our mammillary analysis described the behavior of less soluble anesthetics such as isoflurane well, but that of highly soluble anesthetics such as methoxyflurane less well.

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Several reasons suggest that aging should affect the pharmacokinetics of volatile anesthetics (1). Such a change in kinetics is of interest because elderly patients are a growing segment of the surgical population. They are subject to a greater incidence of disease and a lower reserve of vital organ function, and may be more susceptible to depression from anesthesia (2). Total body weight and lean body mass decrease with aging (3), whereas the percentage of body fat (4,5) and the solubility of anesthetics in tissues (6) increase. These factors should increase the apparent volume of distribution in the elderly, especially for anesthetics markedly soluble in fat. Additionally, decreased hepatic function (1) together with decreased pulmonary gas exchange (secondary to lower metabolic rate) (3) may decrease anesthetic

clearance with age. Finally, decreased cardiac output in the elderly decreases tissue perfusion, increases tissue time constants, and may be associated with an altered regional distribution of anesthetics. For these reasons, we compared the pharmacokinetics of four volatile anesthetics in young and aged patients.

Methods

With prior approval from the Committee on Human Research at the University of California at San Francisco and written informed consent, we studied 18 healthy (ASA physical status I or II) patients. The aged patients, two men and nine women, were 73.2 ± 3.1 yr old (range 59–87 yr) and weighed 72.7 ± 2.9 kg (mean \pm SEM). The young patients, three men and four women, were aged 31 ± 1.8 yr (range 24–37 yr) and weighed 65.2 ± 3.0 kg (mean \pm SEM). Patients in both groups had uneventful surgeries for various lower abdominal operations. Detailed methodology for the present study was reported previously (7), as were the hybrid rate constants, estimates

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Address correspondence to Dr. Eger, Department of Anesthesia, University of California, 455 Sciences, Box 0464, Third and Parnassus Avenues, San Francisco, CA 94143.

of metabolism from mass balance, and anesthetic recovery data from the seven young patients (7).

After premedication with morphine and diazepam, anesthesia was induced with 2-4 mg/kg of thiopental and 2-5 μ g/kg of fentanyl. Pancuronium or vecuronium was used as needed to facilitate endotracheal intubation and to maintain muscle relaxation. Ventilation via a nonrebreathing circuit was adjusted to maintain a normal end-tidal partial pressure of carbon dioxide as confirmed by mass spectrometry.

After establishment of normocapnia, the inspired gas was changed from 100% O₂ to 65%-70% N₂O, balance O₂. Inspired and end-tidal N₂O concentrations were measured by mass spectrometry. After 30 min of equilibration, the end-tidal partial pressure of N₂O reached 98.0% of the inspired partial pressure. Isoflurane (0.365% \pm 0.009%), enflurane (0.568% \pm 0.020%), halothane (0.232% \pm 0.009%), and methoxyflurane (0.0658% \pm 0.0085%), each at approximately 0.3 MAC, were then added to the stream of N₂O for exactly 30 min. To minimize any impact of the second gas effect, the inspired concentration of N₂O was decreased by 5% (i.e., to 60%-65%) concurrent with introduction of the potent inhaled anesthetic agents. After 30 min, administration of the potent inhaled agents was discontinued, and anesthesia was maintained for the duration of the operation with fentanyl, thiopental, and 60%-65% N₂O.

During the 30-min administration period, gas samples were obtained for determination of the fractional concentration of anesthetic inspired (Fi), in the alveoli (FA) (i.e., end-tidal gas), and in mixed expired gases (FM). Fi samples were collected proximal to the nonrebreathing valve. FA samples were collected through a catheter with the tip placed near the tracheal end of the endotracheal tube. The endotracheal tube was connected to the nonrebreathing valve with a length of flexible Teflon tubing with an internal volume of approximately 100 mL. We used Teflon to minimize the absorption and release of anesthetic that occur with plastics such as polyethylene, and the additional 100 mL of dead space prevented the contamination of FA samples with inspired gas. Expired gases were conducted via flexible Teflon tubing to an aluminum mixing chamber, and FM samples were drawn distal to this chamber. All gas samples were collected in 50-mL glass syringes, which were stored upright (to produce a slight positive pressure) until analyzed.

To define the pharmacokinetics of the potent volatile anesthetics during administration, end-tidal (FA) samples were collected during administration at the first five breaths after the start of administration and subsequently at 0.75, 1, 1.5, 2, and 3 min. FA and Fi

samples were collected at 5, 7, 10, 20, and 30 min. Fi samples were not collected during the first 3 min for logistic reasons; instead, the Fi values measured at 10, 15, and 20 min were averaged, and this value was used as the Fi for the first 3 min. Because of delayed washin of the mixing chamber, adequate FM samples could not be obtained during the first 3 min. Values for FM during this interval were estimated by the following formula, using the measured or calculated values for FA and Fi and assuming a constant relationship between FA, FM, and Fi:

$$FM = f_A FA + f_D Fi,$$

where f_A equals the fractional alveolar ventilation and f_D equals the fractional dead-space ventilation. f_A and f_D are the average values calculated from the 10-, 15-, and 20-min samples using this same formula. That is, $1 - f_A$ was substituted for f_D and the equation solved for f_A , then $1 - f_D$ was substituted for f_A and the equation solved for f_D .

During elimination (i.e., after administration of the anesthetic vapors was discontinued), we drew samples for FA and FM determination at the same intervals used during the 30 min of administration. Samples were drawn subsequently at approximately 40, 50, 60, 75, 90, 105, 120, 150, 200, 400, 600, 800, 1200, and 2700 min and then once a day for 3-10 days. Minute ventilation (VE) was measured at these sampling times using a water-seal spirometer. To ensure that the inspired concentration of the four anesthetics was zero, the delivery and expiratory tubing were changed at the start of elimination. Similarly, samples taken after the first 2-4 h of elimination were collected in "fresh" glass syringes that had not been used to draw samples at the higher anesthetizing concentrations. The sampling protocol was interrupted briefly at the end of surgery and during extubation. Gas samples were not collected after extubation until the patients were awake enough to cooperate. These samples were obtained with the patients breathing through a mouthpiece and a low-resistance nonrebreathing valve connected by Teflon tubing to a mixing chamber. Noseclips were used to prevent breathing through the nose when the mouthpiece was used.

To separate and detect isoflurane, enflurane, halothane, and methoxyflurane in the gas samples, we used a dual-column gas chromatograph (Tracor model 550). Each column was composed of 10% SF 96 on Chromasorb WHP, 68/80 mesh, 0.32 cm \times 6.1 m. A stream of nitrogen carrier gas was delivered at 45 mL/min through the column to a flame ionization detector at 200°C, which was supplied by hydrogen at 40 mL/min and by air at 280 mL/min. One column was maintained at 30°C and was used to separate isoflurane, enflurane, and halothane, which had re-

tention times of 3, 3.5, and 5 min, respectively. The second column was kept at 65°–70°C and was used to separate methoxyflurane from the other three anesthetics. Results for each anesthetic were recorded separately on a dual-channel strip recorder. Peak heights were proportional to anesthetic concentration over the entire range of concentrations studied. Calibrations using secondary (tank) standards were obtained at regular intervals during each study.

The ratio of F_A to F_I (F_A/F_I) was used to define the administration of anesthetic. The ratio of F_A to F_{A_0} (F_A/F_{A_0}) was used to define the elimination of anesthetic. F_{A_0} is the alveolar concentration of anesthetic immediately before discontinuation of anesthetic administration. Multiexponential (multicompartment) functions of the form

$$\sum_{i=1}^n \frac{A_i}{L_i} (1 - e^{-L_i t})$$

and

$$\sum_{i=1}^n A_i e^{-L_i t}$$

were fit to the administration and elimination data, respectively, using least-squares analysis (BMDP statistical package [8]). The 18 patients \times 4 anesthetics yielded a total of 72 data sets. We fit equations (models) with successively more exponents (interpreted as compartments) to each data set. The function having the greatest number of compartments (highest n) that significantly decreased the residual sum of squares from the function having one less compartment ($n - 1$) was considered to provide the "best fit" ($P < 0.05$, F-test, [9]).

Hybrid time constants ($1/L_i$) were determined for each compartment. The effect of age on the hybrid time constants was assessed using linear regression [10,11]. We used a t -test to determine if the slope of each regression differed significantly from 0.

Mammillary rate constants were determined for each data set using a five-compartment mammillary model (Figure 1) (BMDP ordinary least-squares regression analysis [8]). This model was fit simultaneously to the logarithm of the concentration of anesthetics in the end-tidal gas (F_A) and the logarithm of the rate of excretion of the anesthetics through the lungs for each of the young and elderly patients. Fitting both the administration and elimination data simultaneously enabled us to determine the rate constant for the metabolism of the anesthetics through the second compartment. Five differential equations were used to describe the rate of change of the concentration of anesthetic in each compartment. A Fortran subroutine incorporating a differential

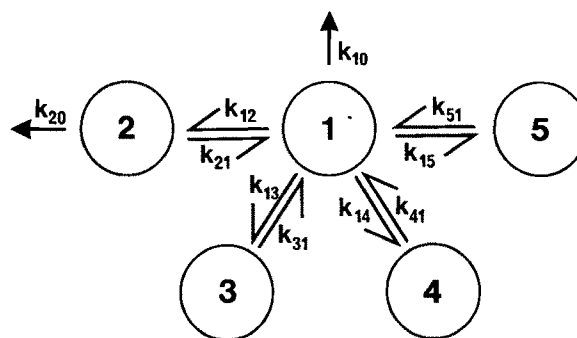


Figure 1. The five-compartment model shown in this schematic was used in the mammillary analysis of our data for isoflurane, enflurane, halothane, and methoxyflurane. Rate constants k_{10} and k_{20} represent the elimination of anesthetic by exhalation and metabolism, respectively. Rate constants k_{ij} represent the rate of intercompartmental transfer of anesthetics.

equation solver was used to integrate the differential equations (12). These data analyses yielded estimates of the volume of the central compartment, the elimination rate constants (k_{10} and k_{20}), and the intercompartmental transfer rate constants (k_{ij} and k_{ji} , where $j = 2, 3, 4, 5$) (see Figure 1). We modeled anesthetic elimination from two sites: the central compartment (lungs, k_{10}) and the second compartment (vessel-rich group or liver, k_{20}). Similar analyses of our data using a four- or six-compartment mammillary function produced a statistically inferior fit as determined by the F-ratio test (9).

We used mammillary rate constants to estimate tissue perfusions and volumes for each of the kinetically defined compartments. For the purposes of this calculation, we speculated on the physiologic identity of each kinetic compartment and used the known tissue/blood and tissue/gas partition coefficients for each anesthetic for each tissue group. We assumed that the first compartment was the pulmonary functional residual capacity, lung tissue volume, and pulmonary capillary blood volume. We assumed the second and third compartments were the vessel-rich group and muscle group, respectively, and the fourth and fifth compartments were fat. To estimate blood flow ($\text{mL} \cdot 100 \text{ mL tissue}^{-1} \cdot \text{min}^{-1}$), we multiplied the corresponding mammillary rate constant (i.e., k_{j1} , where $j = 2, \dots, 5$) by the known tissue/blood partition coefficient (6,13) and by 100. To estimate tissue volume, we multiplied the volume of the central compartment (V_1) by the ratio of the corresponding ingress and egress mammillary rate constants [i.e., k_{1j}/k_{i1} (where $j = 3, 4, 5$) and $k_{12}/(k_{20} + k_{21})$] for the vessel-rich tissues and divided the result by the tissue/gas partition coefficient (6) appropriate to each tissue. We used linear regression analysis to determine the effect of age on each of the resulting tissue perfusion and volume estimates (10).

The total body clearance of each anesthetic was calculated by dividing the total dose of anesthetic administered by the area under the alveolar administration and elimination curves. We estimated the area under the curve for the plot of alveolar concentration (y-axis) versus time (x-axis) using the trapezoidal rule. Elimination of anesthetic from the last data point on the curve until time infinity was extrapolated by taking the ratio of the last alveolar concentration of anesthetic and the estimate of the terminal hybrid rate constant. We used a linear regression analysis of the resulting clearance estimates to determine the effect of age on each (10).

We compared our estimates of the tissue volumes for the fifth compartment (assumed to be fat) derived from the mammillary rate constants against an independent estimate of body fat derived from anthropometric measurements. The latter were derived using measures of skinfold thickness as described by Durnin and Womersley (14). Skinfold thickness was measured in triplicate at four different locations (biceps, triceps, subscapular, and suprailiac). The sum of the average of these measurements for each patient was then substituted into the appropriate (for sex and age) linear equation to arrive at the estimate of total body fat volume. We used linear regression analysis (10) to compare the kinetic estimate of fifth-compartment volume (assumed to be fat) determined from mammillary rate constants with the volume of fat estimated by anthropometric measures for each volatile anesthetic.

Finally, we calculated the volume at steady state for each volatile anesthetic for young and old patients using the mammillary rate constants and the following formula:

$$Vd_{ss} = V_1 \left(1 + \frac{k_{12}}{k_{21} + k_{20}} + \frac{k_{13}}{k_{31}} + \frac{k_{14}}{k_{41}} + \frac{k_{15}}{k_{51}} \right),$$

where Vd_{ss} is the apparent volume at steady state and k_{1j} and k_{j1} are the corresponding mammillary rate constants. We used a linear regression analysis to correlate the volume at steady state for each anesthetic with age and with fat volume as estimated from anthropometric measurements.

Results

The alveolar anesthetic concentration increased during administration in inverse proportion to the solubility of each anesthetic in the blood (Figure 2). In contrast, alveolar anesthetic concentration during elimination decreased coincidentally for all four anesthetics unrelated to solubility (Figure 3). The terminal elimination rate was similar for all four anesthetics and linear for all patients. After 24 h, the rate of anesthetic elimination slowed for the aged patients

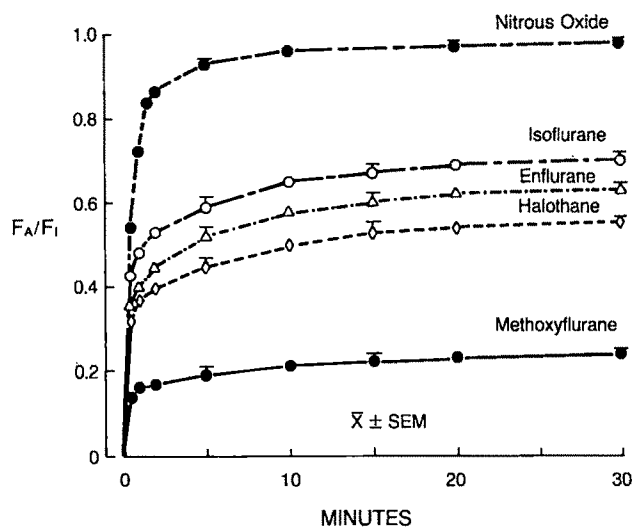


Figure 2. The rise in the ratio of alveolar to inspired anesthetic concentration (F_A/F_I) for the aged group of patients ($n = 11$) follows the course predicted from solubility and perfusion. Values are mean \pm SEM.

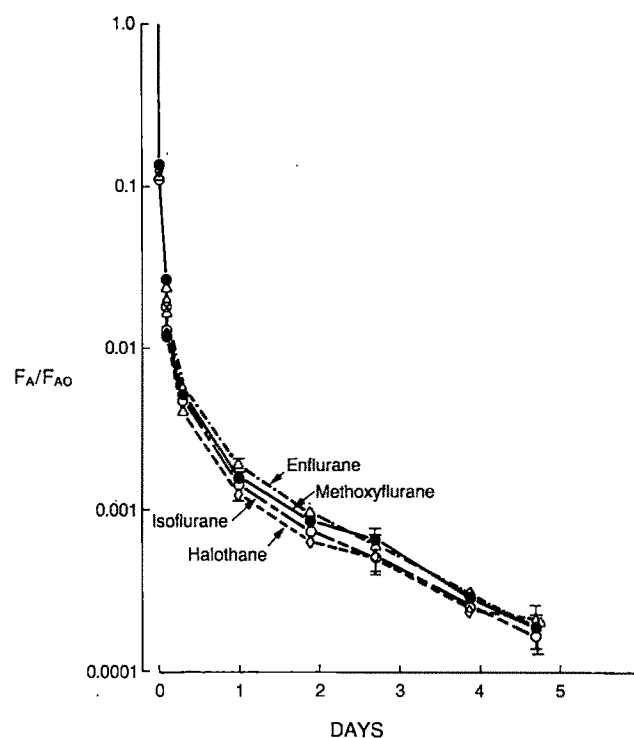


Figure 3. The decline in the anesthetic concentration for the aged patients is plotted as the ratio of the alveolar concentration (F_A) to the alveolar concentration when anesthetic administration ceased (F_{A0}) ($n = 11$). Values are mean \pm SEM.

compared with young patients. Results for isoflurane and halothane are typical of all four anesthetics and are shown in Figure 4. Similar results obtained for enflurane and methoxyflurane are not pictured here because they overlie the other two curves and obscure the result.

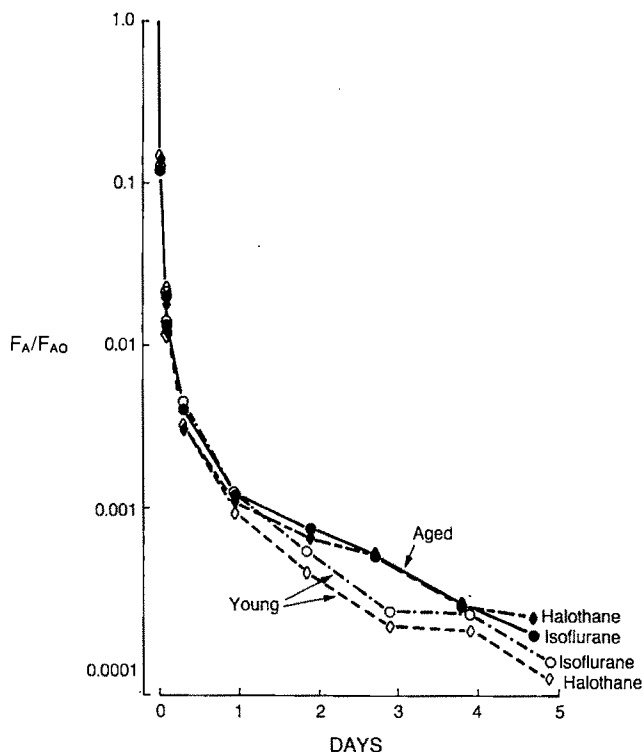


Figure 4. Elimination of halothane and isoflurane from aged and young patients. The decline in anesthetic concentration is expressed as the ratio of alveolar concentration at a given time (F_A) to the alveolar concentration when administration ceased (F_{A0}) ($n = 11$ in aged group, $n = 7$ in young group). Values are mean \pm SEM.

Alveolar elimination data for 65 of 72 data sets (4 anesthetics \times 18 patients) was best fit to a five-compartment exponential function (Table 1). The remaining seven data sets (six for methoxyflurane and one for enflurane) were best fit by either a four- or six-exponential function or were incomplete because of limited collections. The hybrid time constants were similar when compared between anesthetics (Table 1). The L_5 hybrid time constants for all four anesthetics increased with age ($P \leq 0.05$).

The central volume of distribution (V_1) as determined by mammillary rate constant analysis decreased with age for all four anesthetics, but the trend was weak ($P = 0.11$ – 0.23 ; $r^2 = 3\%$ – 12%). The mammillary rate constants were not significantly affected by aging except for k_{51} (Table 2). The k_{51} mammillary rate constants decreased with age for all four anesthetics ($P = 0.01$ – 0.53 ; $r^2 = 5\%$ – 27%), but reached statistical significance ($P \leq 0.05$) only for the two least soluble anesthetics, isoflurane and enflurane. The k_{20} mammillary rate constants reflecting metabolism did not vary with age but increased proportionately with anesthetic solubility for all four anesthetics ($P \leq 0.05$).

Tissue perfusion was estimated for each compartment by making an assumption: that each kinetic compartment represents a known tissue group (Table

3) (see Discussion). Perfusion estimates for the second compartment decreased with age for all four anesthetics but reached statistical significance only for the two insoluble anesthetics, isoflurane and enflurane ($P \leq 0.05$; $r^2 = 18\%$ – 28%). Perfusion estimates decreased with age for all four anesthetics for both the fourth and fifth compartments ($P = 0.01$ – 0.57 ; $r^2 = 0\%$ – 28%), but the effect was strong only for the two less soluble anesthetics, isoflurane and enflurane ($P \leq 0.05$; $r^2 = 26\%$ – 28%).

Table 4 shows the volume (liters) of each compartment, estimated by assuming each kinetic compartment represents a known tissue group. The estimated volumes of the fourth and fifth compartments increased with age for all four anesthetics. This trend, however, reached statistical significance ($P \leq 0.05$) only for isoflurane and enflurane (fourth compartment) and halothane (fifth compartment). Tissue volume estimates were inversely proportional to anesthetic solubility; volumes estimated for methoxyflurane were smaller than those for the other three anesthetics.

Total body clearance for all four anesthetics decreased with age, but the trends failed to reach statistical significance ($P = 0.38$ – 0.57 ; $r^2 \leq 1\%$). Clearance values increased in proportion to anesthetic solubility (Table 5). Those for halothane and methoxyflurane were significantly higher than those for isoflurane and enflurane ($P \leq 0.05$).

Total body fat, as measured by anthropometric measurements, correlated strongly with age ($P \leq 0.00$; $r^2 = 68\%$). Estimates of total body fat from kinetic data (the volume of the fourth added to the volume of the fifth compartment) also increased with age for all four anesthetics ($P = 0.04$ – 0.19 ; $r^2 = 9\%$ – 23%). Kinetic estimates of total body fat volumes correlated with anthropometric measurements for all four anesthetics ($P \leq 0.00$; $r^2 = 69\%$ – 79%).

The apparent volume of distribution at steady state (Table 6) increased with age for all four anesthetics ($P = 0.04$ – 0.20 ; $r^2 = 9\%$ – 23%). The trend was strongest for methoxyflurane ($P \leq 0.04$) and isoflurane and halothane ($P \leq 0.05$), and weaker for enflurane ($P \leq 0.08$). The volume of distribution at steady state correlated well with the estimates of fat by anthropometric measurements for all four anesthetics ($P = 0.001$ – 0.03 ; $r^2 = 56\%$ – 72%). $V_{d,ss}$ was directly proportional to the anesthetic solubility, the $V_{d,ss}$ for methoxyflurane being two to three times greater than that for other, less soluble anesthetics.

Discussion

Our present results and those from previous studies (7,15) indicate that a sum of five exponentials best describes elimination of volatile anesthetics. Such a

Table 1. Hybrid Time Constants ($1/L_i$) for the Five-Compartment Exponential Function of Alveolar Elimination

Compartment	Isoflurane (min)	Enflurane (min)	Halothane (min)	Methoxyflurane (min)
Elderly patients ^a	(n = 11)	(n = 10)	(n = 11)	(n = 8)
1	0.27 ± 0.03	0.23 ± 0.02	0.23 ± 0.02	0.09 ± 0.03
2	8.12 ± 0.52	7.62 ± 0.56	7.62 ± 0.38	8.51 ± 0.84
3	61.16 ± 8.94	72.05 ± 7.73	91.58 ± 14.42	64.39 ± 6.72
4	521 ± 59.7	559 ± 90.5	398 ± 121	588 ± 83.0
5	3704 ± 411 ^c	3333 ± 222 ^d	3846 ± 444 ^e	4167 ± 868 ^f
Young patients ^b	(n = 7)	(n = 7)	(n = 7)	(n = 4)
1	0.29 ± 0.02	0.25 ± 0.02	0.27 ± 0.01	0.13 ± 0.02
2	6.13 ± 0.41	5.99 ± 0.54	7.41 ± 0.52	8.26 ± 0.44
3	56.2 ± 2.81	57.5 ± 2.74	52.4 ± 4.20	55.8 ± 14.0
4	405 ± 36	433 ± 28	347 ± 53	356 ± 23
5	2037 ± 398 ^c	1942 ± 320 ^d	2294 ± 458 ^e	2353 ± 327 ^f

Values are mean ± SEM.

^aAge, 73.2 ± 3.1 yr; weight, 72.7 ± 3.1 kg.^bAge, 31 ± 1.8 yr; weight, 65.2 ± 3.0 kg.^{c,d,e,f}These pairs of values are statistically different ($P \leq 0.05$).

Table 2. Estimated Mean Volumes of the Central Compartment and Mammillary Rate Constants

Compartment	Isoflurane	Enflurane	Halothane	Methoxyflurane
Elderly patients ^a	(n = 11)	(n = 11)	(n = 9)	(n = 7)
V ₁	1.71 ± 0.14	1.77 ± 0.16	1.83 ± 0.22	3.12 ± 0.42
k ₁₀	1.81 ± 0.15	1.83 ± 0.16	1.99 ± 0.25	1.39 ± 0.20
k ₁₂	1.03 ± 0.11	1.39 ± 0.16	1.61 ± 0.15	3.31 ± 0.32
k ₁₃ × 10 ⁻¹	3.20 ± 0.30	4.08 ± 0.33	4.07 ± 0.80	7.74 ± 1.65
k ₁₄ × 10 ⁻¹	3.23 ± 0.49	3.63 ± 0.55	2.89 ± 0.46	4.63 ± 1.15
k ₁₅ × 10 ⁻¹	2.22 ± 0.37	2.61 ± 0.54	3.08 ± 0.65	5.01 ± 1.25
k ₂₁ × 10 ⁻¹	1.68 ± 0.12	1.87 ± 0.14	1.90 ± 0.64	1.31 ± 0.45
k ₃₁ × 10 ⁻²	2.02 ± 0.33	1.87 ± 0.22	2.32 ± 0.73	2.69 ± 0.77
k ₄₁ × 10 ⁻³	2.22 ± 0.27	2.21 ± 0.29	2.51 ± 0.36	2.68 ± 0.62
k ₅₁ × 10 ⁻⁴	3.06 ± 0.23 ^c	3.52 ± 0.26 ^d	3.33 ± 0.40	3.45 ± 0.61
k ₂₀ × 10 ⁻²	0.20 ± 0.14	0.67 ± 0.39	2.57 ± 0.56	11.13 ± 4.62
Young patients ^b	(n = 7)	(n = 7)	(n = 7)	(n = 4)
V ₁	1.80 ± 0.12	1.89 ± 0.13	2.03 ± 0.13	2.83 ± 0.27
k ₁₀	1.76 ± 0.18	1.70 ± 0.20	1.71 ± 0.23	1.25 ± 0.14
k ₁₂	1.35 ± 0.08	1.72 ± 0.07	1.88 ± 0.07	4.99 ± 0.32
k ₁₃ × 10 ⁻¹	3.14 ± 0.31	4.39 ± 0.48	3.24 ± 0.41	4.67 ± 0.80
k ₁₄ × 10 ⁻¹	2.47 ± 0.31	2.88 ± 0.38	2.17 ± 0.21	4.22 ± 0.55
k ₁₅ × 10 ⁻¹	1.68 ± 0.34	1.84 ± 0.44	1.38 ± 0.32	3.57 ± 0.97
k ₂₁ × 10 ⁻¹	2.36 ± 0.16	2.46 ± 0.23	1.99 ± 0.25	1.18 ± 0.18
k ₃₁ × 10 ⁻²	2.08 ± 0.11	2.06 ± 0.10	2.61 ± 0.77	2.50 ± 0.56
k ₄₁ × 10 ⁻³	3.05 ± 0.37	2.75 ± 0.29	3.68 ± 0.82	3.94 ± 1.33
k ₅₁ × 10 ⁻⁴	5.40 ± 1.02 ^c	5.78 ± 0.94 ^d	4.70 ± 0.88	4.38 ± 0.88
k ₂₀ × 10 ⁻²	0.11 ± 0.11	1.04 ± 0.31	3.09 ± 0.62	7.56 ± 0.73

V₁, volume of central compartment in liters; k_{ij}, mammillary rate constants (min⁻¹).

Values are mean ± SEM.

^aAge, 73.2 ± 3.1 yr; weight, 72.7 ± 3.1 kg.^bAge, 31.0 ± 1.8 yr; weight, 65.2 ± 3.0 kg.^{c,d}These pairs of values are statistically different from one another ($P \leq 0.05$).

sum of exponentials may describe several different pharmacokinetic models, and any of these models will yield a unique set of mammillary rate constant values (16). Well-known dangers are associated with ascribing physiologic significance to pharmacokinetic parameters derived from these models (17). Nevertheless, a specific physiologic interpretation of the

models can be supported by incorporating what is known of physiologic and anatomic reality into the modeling process. For this reason, we assigned physiologic and anatomic identities to our mammillary model (Tables 3 and 4) based on accepted theory and known values for tissue perfusion, volume, and solubility that were not acquired by kinetic methods

Table 3. Mean Perfusions Estimated for Each Kinetic Compartment Assuming That Each Compartment Represents a Known Tissue Group

Compartment	Isoflurane (mL·100 mL tissue vol ⁻¹ ·min ⁻¹)	Enflurane (mL·100 mL tissue vol ⁻¹ ·min ⁻¹)	Halothane (mL·100 mL tissue vol ⁻¹ ·min ⁻¹)	Methoxyflurane (mL·100 mL tissue vol ⁻¹ ·min ⁻¹)	Literature
Elderly patients ^a	(n = 11)	(n = 11)	(n = 9)	(n = 7)	
2	30.06 ± 2.15 ^c	24.26 ± 1.85 ^d	23.78 ± 2.61 ^e	11.21 ± 1.18	60.7 ^f
3	3.07 ± 0.50	2.04 ± 0.24	3.33 ± 1.06	4.14 ± 1.19	2.5 ^f
4	11.79 ± 1.41	9.05 ± 1.18	15.25 ± 2.19	14.04 ± 3.28	—
5	1.63 ± 0.12 ^g	1.44 ± 0.10 ^h	2.02 ± 0.24	1.81 ± 0.32	2.4 ^f
Young patients ^b	(n = 7)	(n = 7)	(n = 7)	(n = 4)	
2	42.20 ± 2.80 ^c	31.92 ± 2.97 ^d	37.03 ± 4.69 ^e	15.28 ± 2.38	60.7 ^f
3	3.16 ± 0.17	2.25 ± 0.11	3.76 ± 1.11	3.85 ± 0.87	2.5 ^f
4	16.18 ± 1.94	11.27 ± 1.18	22.31 ± 5.00	20.66 ± 6.96	—
5	2.87 ± 0.54 ^g	2.37 ± 0.38 ^h	2.85 ± 0.53	2.30 ± 0.46	2.4 ^f

Values are mean ± SEM.

^aAge, 73.2 ± 3.1 yr; weight, 72.7 ± 3.1 kg.^bAge, 31 ± 1.8 yr; weight, 65.2 ± 3.0 kg.^{c,d,e,g,h}These pairs of values are statistically different from one another (*P* ≤ 0.05).^fThese values compiled from Mapleson (19) and Guyton (20).**Table 4.** Mean Volume Estimated for Each Kinetic Compartment Assuming That Each Compartment Represents a Known Tissue Group

Compartment	Isoflurane (L)	Enflurane (L)	Halothane (L)	Methoxyflurane (L)	Literature
Elderly patients ^a	(n = 11)	(n = 11)	(n = 9)	(n = 7)	
2	3.93 ± 0.45	3.68 ± 0.40	3.44 ± 0.45	3.04 ± 0.55	3.6 ^c
3	14.56 ± 2.24	18.41 ± 2.46	10.32 ± 2.09	4.84 ± 1.59	23.4 ^c
4	3.33 ± 0.46	3.55 ± 0.45 ^d	1.39 ± 0.24 ^e	0.64 ± 0.11	—
5	15.92 ± 2.14	14.85 ± 2.01	9.59 ± 1.16 ^f	5.24 ± 1.10	13.5 ^c
Young patients ^b	(n = 7)	(n = 7)	(n = 7)	(n = 4)	
2	3.93 ± 0.30	3.88 ± 0.41	3.64 ± 0.53	3.67 ± 0.53	3.6 ^c
3	12.20 ± 1.19	17.41 ± 1.53	7.99 ± 1.36	2.86 ± 1.08	23.4 ^c
4	2.01 ± 0.33	2.40 ± 0.35 ^d	0.90 ± 0.17 ^e	0.45 ± 0.11	—
5	9.74 ± 3.27	9.53 ± 3.42	5.09 ± 1.70 ^f	3.36 ± 1.27	13.5 ^c

Values are mean ± SEM.

^aAge, 73.2 ± 3.1 yr; weight, 72.7 ± 3.1 kg.^bAge, 31 ± 1.8 yr; weight, 65.2 ± 3.0 kg.^cValues (liters) are compiled from report of the Task Group on Reference Man (21).^{d,e,f}These pairs of values are statistically different from one another (*P* ≤ 0.05).

(6,13,18–21). In doing so, we acknowledge that our study does not prove these identifications, but rather these assumptions allow us to interpret our kinetic observations in the framework of a familiar physiologic model (Figure 1). In the text that follows, the reader must realize that anatomic references for kinetic observations are based not on absolute identification of the named tissues, but rather on reasonable assumptions.

FA/FI increased rapidly for all anesthetics (including N₂O) as would be predicted from their relative solubilities in blood and tissues (Figure 2). These administration data support at best a two-compartment exponential function analysis. We observed no effect owing to aging during the administration phase. The inability to define an effect owing to aging in this phase is probably due to the limited number of

observations available during the shorter (0.5 h) administration period.

FA/FA₀ ratios, in contrast to the FA/FI data, contain information sufficient to support a five-compartment exponential function fit. Most of the changes owing to aging were observed in parameters derived from the fourth and fifth compartments and would not have been detected if only the administration data were considered. These "richer" elimination data (5–7 days) show that aged patients eliminate anesthetics more slowly after the first 24 h (Figure 4). This observation is consistent with an increased ratio of fat/lean body weight (22) and decreased perfusion per unit volume of fat in the aged (Table 3).

All four anesthetics were eliminated at about the same rate (Figure 3) despite predicted differences based on anesthetic solubility in blood and tissue.

Table 5. Total Body Clearances of Isoflurane, Enflurane, Halothane, and Methoxyflurane

	Isoflurane (mL/min)	Enflurane (mL/min)	Halothane (mL/min)	Methoxyflurane (mL/min)
Elderly patients ^a	(n = 11) 2802.1 ± 219.7	(n = 11) 2927.6 ± 205.0	(n = 11) 3644.9 ± 225.4 ^c	(n = 11) 7756.2 ± 487.1 ^c
Young patients ^b	(n = 7) 3032.3 ± 147.1	(n = 7) 3166.1 ± 151.5	(n = 7) 3879.9 ± 170.4 ^d	(n = 7) 8260.1 ± 67.0 ^d

Values are mean ± SEM.

^aAge, 73.2 ± 3.1 yr; weight, 72.7 ± 3.1 kg.^bAge, 31 ± 1.8 yr; weight, 65.2 ± 3.0 kg.^{c,d}These values are significantly different from those for the other anesthetics in each age group ($P \leq 0.05$).**Table 6.** Apparent Total Body Volumes of Distribution at Steady State for Isoflurane, Enflurane, Halothane, and Methoxyflurane

	Isoflurane (L)	Enflurane (L)	Halothane (L)	Methoxyflurane (L)
Elderly patients ^a	(n = 11) 1536.9 ± 167.3 ^c	(n = 11) 1615.9 ± 170.0 ^d	(n = 9) 1821.9 ± 211.7 ^e	(n = 7) 5123.5 ± 1017.8
Young patients ^b	(n = 7) 949.8 ± 265.1 ^c	(n = 7) 1066.0 ± 303.4 ^d	(n = 7) 1012.7 ± 279.9 ^e	(n = 4) 3347.1 ± 1136.7

Values are mean ± SEM.

^aAge, 73.2 ± 3.1 yr; weight, 72.7 ± 3.1 kg.^bAge, 31 ± 1.8 yr; weight, 65.2 ± 3.0 kg.^{c,d,e}These pairs of values are significantly different from one another ($P \leq 0.05$).

This unexpected homogeneity of elimination is probably the net result of two independent but complementary elimination processes. The less soluble anesthetics are being redistributed (eliminated) more rapidly than highly soluble anesthetics from the fifth compartment. This is evidenced by larger k_{51} mammillary rate constants and longer hybrid time constants for the less soluble anesthetics. The less soluble anesthetics would be eliminated more quickly than the soluble anesthetics were it not for increased metabolic elimination of the highly soluble anesthetics as evidenced by larger k_{20} mammillary rate constants (Table 2) and total body clearances (Table 5). It seems reasonable to believe that k_{51} may represent elimination of anesthetic from the poorly perfused fat group and that k_{20} probably represents hepatic metabolism of anesthetic (23). It is interesting that whereas k_{51} decreased with age, implying decreased perfusion relative to capacity with age, k_{20} (hepatic metabolism) appeared to be unaffected by aging.

The initial volume of distribution (V_1) decreased with age for all anesthetics, but the trend was weak and the effect did not reach statistical significance. V_1 also decreases with age for the intravenous anesthetics propofol, etomidate, and thiopental (24-26), but these anesthetics differ because estimates of V_1 for these agents do not include pulmonary gas spaces (functional residual capacity). We expected to see a significant increase in V_1 for the volatile anesthetics because of an increased functional residual capacity

with aging. Perhaps this trend was obscured by noise in our data, or perhaps the volatile anesthetics differ from the intravenous anesthetics with respect to V_1 . Alternatively, the increase in closing capacity associated with age may have impaired our ability to adequately assess the true functional residual capacity in the aged.

We used mammillary rate constants to predict tissue perfusions and volumes. This is possible because the metabolism, routes of excretion, and solubilities in blood and tissues are well known for each anesthetic (6,13,18-21). Tissue volumes for the second, third, and fifth compartments approximated the published literature values for the less-soluble anesthetics isoflurane, enflurane, and halothane, circumstantially supporting our assumptions regarding tissue identification. Tissue volume estimates for methoxyflurane, however, were smaller than for the other three anesthetics. The reason for this discrepancy is not clear, but may relate to lipid solubility or metabolism, because methoxyflurane is the most soluble and the most extensively metabolized of the four anesthetics (23).

Our tissue perfusion estimates agreed reasonably well with published estimates of perfusion to the third and fifth compartment (muscle and fat) for all four anesthetics (Table 3) but underestimated perfusion to the second compartment (muscle group) by two to six times. This underestimate for the vessel-rich group may have resulted from intertissue diffu-

sion (27) to adjacent fat (fourth compartment), in effect causing us to underestimate tissue solubility. Perfusion to the second, fourth, and fifth compartments decreased with age for all anesthetics, the trend being strongest for the less soluble anesthetics isoflurane and enflurane.

The most substantial changes with age were observed for the fourth and fifth compartments. The volume of the fourth and fifth compartments increased with age, consistent with increased total body fat in the elderly. Our observation that the sum of the volumes of the fourth and fifth compartments correlated with fat volume as measured by anthropometric methods supports this thesis. Total body fat by anthropometric measurement also increased with age as did the apparent volume of distribution at steady state (V_{dss}).

We speculate that the fourth compartment may represent a thin layer of fat that receives anesthetic by diffusion from adjacent well-perfused tissues (i.e., perinephric fat) (27,28). Compatible with this identification of the fourth compartment is the observation that perfusion to the fourth compartment is intermediate between the vessel-rich group or muscle and fat and is an order of magnitude greater than perfusion to the fifth compartment (Table 3). Delivery of anesthetic to this compartment may be the sum of delivery by perfusion to fat and by intertissue diffusion from the vessel-rich group or muscle. Aging would be expected to delay elimination of anesthetic from the fourth compartment because perfusion to the fourth compartment is decreased with age and because decreased perfusion to the second compartment with age would probably secondarily reduce the rate of additional elimination by intertissue diffusion.

In summary, our results indicate that recovery from anesthesia proceeds more slowly in aged patients. Tissue perfusion estimates are decreased in the elderly, and estimates of tissue volume are increased compatible with an increase in total body fat mass with age. The apparent volume of distribution for volatile anesthetics increases with age.

Isoflurane (Forane) and enflurane (Ethrane) for this study were donated by Anaquest. Halothane (Fluothane) was donated by Ayerst Laboratories.

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Modifications by Halothane of Responses to Acute Hypoxia in Systemic Vascular Capacitance, Resistance, and Sympathetic Nerve Activity in Dogs

Hiroyuki Arimura, MD, Zeljko J. Bosnjak, PhD, Sumio Hoka, MD, and John P. Kampine, MD, PhD

Departments of Anesthesiology and Physiology, The Medical College of Wisconsin and Zablocki VA Medical Center, Milwaukee, Wisconsin

To examine the effects of halothane on segmental vascular responses to hypoxia, we used cardiopulmonary bypass with venous outflow divided into three compartments (splanchnic, coronary, and "other") in dogs anesthetized with pentobarbital sodium. The reservoir volume changes represented the inverted changes in systemic blood volume (SBV). In addition, sympathetic efferent nerve activity (SENA) was simultaneously recorded from the ventral ansa subclavian nerve. Experiments were done in two groups: severe hypoxia (P_{O_2} of 19 mm Hg) and moderate hypoxia (P_{O_2} of 50 mm Hg). Hypoxia provoked a significant decrease in SBV of 22.3 ± 3.1 mL/kg and 10.5 ± 1.6 mL/kg during severe and moderate hypoxia, respectively. Two percent end-tidal halothane attenuated the decrease in SBV to 10.3 ± 1.3 mL/kg during severe hypoxia, and 1% halothane attenuated the decrease to 3.7 ± 1.4 mL/kg during moderate hypoxia. Subsequent chemoreceptor denervation in the presence of 1% halothane completely abolished the moderate hypoxia-induced decrease in SBV. In the presence of halothane, vascular resistance during

hypoxia was significantly less than that during control conditions. Sympathetic efferent nerve activity increased significantly during severe and moderate hypoxia by about 180% and 55%, respectively. During severe hypoxia, halothane did not cause any change in the response of SENA, whereas during moderate hypoxia, halothane tended to decrease SENA, but not significantly, and subsequent chemoreceptor denervation completely abolished the increase in SENA. Coronary resistance showed a hypoxia-induced reduction that was not influenced by halothane. These results suggest that acute hypoxia causes a decrease in SBV dependent on the severity of hypoxia. Halothane attenuates the responses to moderate hypoxia in both resistance and capacitance vessels but does not completely abolish the decrease in vascular capacitance. During severe hypoxia, halothane (1% and 2%) does not depress the hypoxia-induced increase in sympathetic discharge, and the suppression of the vascular response by halothane is probably due to its peripheral (vascular) actions.

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Acute hypoxia, a critical and sometimes fatal complication during anesthesia, has been reported to increase heart rate (1), blood pressure (1,2), and cardiac output (2,3). However, Manninen and Knill (4) have demonstrated that neither heart rate nor blood pressure is a reliable indicator for recognition of acute hypoxia during either halothane or enflurane anesthesia, suggesting that these anesthetics attenuate the cardiovascular response to hypoxia.

Vascular capacitance, as well as vascular resistance and cardiac performance, are important determinants of cardiovascular function. It has been reported that acute hypoxia decreases systemic blood volume by 16 mL/kg (5) and increases the mean circulatory filling pressure by 2.5 mm Hg (6). Such a large decrease in systemic blood volume is due to neural mechanisms. For instance, our previous study demonstrated acute decrease in systemic blood volume of 23 mL/kg after acute, severe hypoxia, which was attenuated by 60% and 83% after chemoreceptor denervation and after hexamethonium infusion, respectively (7). However, the effects of anesthetics on the vascular capacitance response to hypoxia have not been reported. One of the purposes of the present study was to examine the effect of halothane on the hypoxic responses, specifically those involving vascular capacitance, resis-

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Address correspondence to Dr. Bosnjak, Medical College of Wisconsin, MFRS, A1000, Milwaukee, WI 53226.

tance, and sympathetic nerve activity, using cardiopulmonary bypass in pentobarbital-treated dogs.

For the analysis of the participation of vascular resistance and capacitance in cardiovascular dynamic changes, cardiopulmonary bypass or right ventricular bypass is a reliable method (5,7-10), because changes in vascular resistance and capacitance can be reflected in the changes in arterial pressure and inverted changes in reservoir volume, respectively, during constant systemic perfusion flow. Furthermore, since Caldini et al. (10) postulated a model of two compartments for the analysis of the effect of epinephrine, cardiopulmonary bypass has been a useful method to divide the venous vascular bed into separate compartments that have different time constants (7,8,11,12). In the present study, therefore, the venous outflow was divided into three compartments, splanchnic, coronary, and "other."

Davies et al. (13) demonstrated that halothane depresses the response of carotid body chemoreceptors to hypoxia and hypercapnia in the cat, suggesting that the depression of chemoreflexes contributes to the effect of halothane on the hypoxic response. As the sympathetic nervous system plays an important role in the vascular responses to hypoxia by eliciting vasoconstriction which counteracts the direct vasodilating effect of hypoxia (14), efferent sympathetic nerve activity was simultaneously recorded as another part of this study. The purpose of these latter studies was to investigate whether changes in sympathetic nerve activity accompanied the observed vascular responses.

Methods

Two series of experiments were done using 11 mongrel dogs (weighing 27.8 ± 1.2 kg): six dogs for the severe hypoxia study and five dogs for the moderate hypoxia study. Each dog was anesthetized with 30 mg/kg of pentobarbital sodium and supplemental doses were given as necessary. The trachea was intubated with a cuffed endotracheal tube and the tube was connected to a Bird Mark 7 respirator for mechanical ventilation with 100% oxygen. The partial pressure of carbon dioxide (P_{CO_2}) was kept between 30 and 40 mm Hg until cardiopulmonary bypass was started. Systemic arterial pressure was continuously measured through a cannula placed in the right axillary artery. To measure venous outflow pressure during cardiopulmonary bypass, catheters were placed in the superior vena cava via the right axillary vein and the inferior vena cava above the renal veins via the right femoral vein for "other" regions and splanchnic regions, respectively. All pressure lines were connected to Statham pressure transducers.

After a median sternotomy and median laparot-

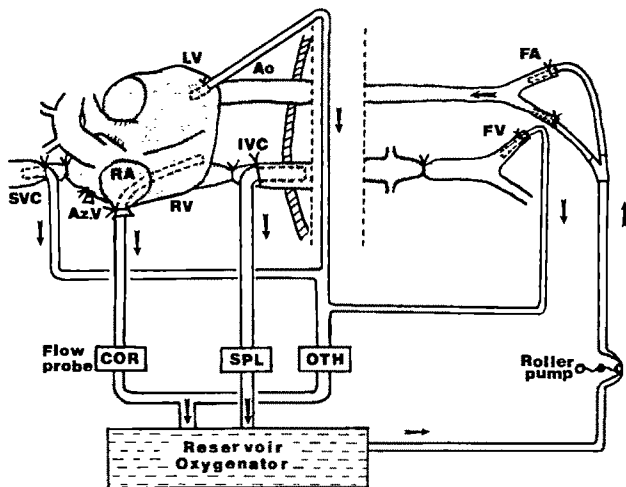


Figure 1. Schematic presentation of the cannulation for the measurements of regional outflows. RA, right atrium; RV, right ventricle; LV, left ventricle; Ao, aorta; SVC, superior vena cava; IVC, inferior vena cava; Az.V, azygos vein; FA, femoral artery; FV, femoral vein; COR, coronary outflow; SPL, splanchnic outflow; OTH, "other" outflow.

omy were completed, cardiopulmonary bypass was instituted using a Sarns roller pump (model 3500) and a Shiley reservoir oxygenator. The roller pump was adjusted to be completely occlusive to maintain a constant perfusion flow rate despite changes in peripheral vascular resistance. Five hundred units per kilogram of sodium heparin and 200 μ g/kg of pancuronium bromide were given intravenously before the venous outflow cannulations. Venous outflow was divided into three compartments: splanchnic, coronary, and other outflow (Figure 1). Splanchnic outflow was drained from the inferior vena cava through a catheter advanced to the middle of the diaphragm; this region was isolated by ligatures around the inferior vena cava below the renal veins and above the hepatic veins. Splanchnic output therefore includes renal blood flow. The superior vena cava and azygos veins were also ligated. Blood outflow through a cannula placed in the right ventricle through the right atrial appendage represented coronary outflow and a small fraction ($\leq 1\%$) contributed by thebesian vein flow. Although coronary outflow pressure was not measured, the right ventricle was confirmed by inspection to be empty throughout the experiment. Venous outflows through catheters placed in the superior vena cava, left ventricular apex, and left femoral vein were joined and represented other outflow. Outflow from each vascular bed was passed through Biotronex electromagnetic flowmeters and drained by gravity into a reservoir oxygenator primed with a mixture of lactated Ringer's solution (2000 mL) and Dextran 40 (1000 mL) with 10,000 U of sodium heparin. Blood flow recordings

were calibrated at the end of each experiment using a timed collected flow. Venous outflow pressure was adjusted by adjusting the height of the reservoir inlet to 5–10 mm Hg and was kept constant throughout the experiment. Systemic perfusion was performed through cannulas placed in both femoral arteries. The perfusion pump was adjusted so that arterial blood pressure was approximately equal to blood pressure before initiation of bypass, the perfusion being maintained thereafter at a constant rate throughout the experiment. Body temperature was maintained at 37°C with a heat exchanger during cardiopulmonary bypass.

Sympathetic efferent nerve activity (SENA) was measured using the left ventral ansa subclavian nerve. The whole nerve was isolated, sectioned, desheathed, and laid across tungsten carbide bipolar electrodes in a warm mineral oil bath. Nerve activity was recorded using a high-impedance differential preamplifier (gain of 100; 0.1–10 kHz passband) followed by a filter amplifier combination. Raw nerve activity was recorded on a Vetter FM tape recorder for later analysis based on moving time average and voltage-to-frequency converter averaging (15) that counted for 2-s intervals. Nerve activity was recorded on a Grass model 7 polygraph simultaneously with measurements of arterial pressure, central venous pressure, and venous outflows from three beds.

Reservoir blood volume, changes of which inversely reflect changes in systemic blood volume, was measured at 30-s intervals by reading the blood level on the reservoir scale to the nearest 10 mL. The relationship between change in real blood volume and change in blood volume measured by graduation on the reservoir was examined in each experiment by adding blood of known volume to the reservoir to determine real blood volume change by correction of the measured change in volume. The average correlation was as follows: real blood volume change = $(0.74 \pm 0.02) \times$ (blood volume change measured by scale on the reservoir). This relation indicated that a measured volume change reflected 135% of a real volume change, and so the real volume change was determined by multiplying the measured reservoir volume change by 0.74.

In both the severe and moderate hypoxia study, hypoxia was applied under three different conditions: control (hypoxia only), 1% halothane, and 2% halothane. To examine the contribution of peripheral chemoreceptors to hypoxia change, we have denervated peripheral chemoreceptors in five dogs and examined the effects of moderate hypoxia and 1% halothane. Aortic chemoreceptor denervation was performed by sectioning the cervical vagosympathetic trunks. The carotid chemoreceptor function was eliminated by painting 5% phenol topically over

the carotid sinus region after the regions were stripped of the sheath and crushed. Adequacy of carotid chemoreceptor denervation was verified by the absence of blood pressure response to the local application of 1 mg of sodium cyanide. The procedure to denervate the chemoreceptor is considered to be inevitably accompanied by some baroreceptor denervation of both carotid sinus and aortic baroreceptors.

Rest periods of at least 20 min were allowed between each exposure to hypoxia. Hypoxia was produced by changing the normal gas mixture, oxygen (6 L/min) and carbon dioxide (0.25 L/min), that was supplied to the oxygenator chamber. To produce severe hypoxia, oxygen (6 L/min) was replaced by nitrogen (6 L/min) for 3.5 min. For moderate hypoxia, a mixture of oxygen (1 L/min), nitrogen (5 L/min), and carbon dioxide (0.25 L/min) was given for 4.5 min. Halothane was vaporized using a Fluotec 3 vaporizer installed in line with a gas mixture supply to the reservoir. Halothane concentrations in blood samples were measured on a Perkin-Elmer Sigma 3B gas chromatograph at 5, 10, and 15 min after the start of readministration of halothane. Sodium bicarbonate (1 mEq/kg) was added to the reservoir soon after each exposure to hypoxia to maintain optimal pH and base excess. During exposure to hypoxia, blood samples were obtained from the reservoir for blood gas analysis.

All data are expressed as mean \pm standard error of the mean. Statistical analyses of blood gas tensions (Table 1) and baseline hemodynamic data (Table 2) were first performed with a two-way analysis of variance, and a paired *t*-test was done if the *F*-test was significant. For the analysis of the time-course (Figures 2–5), first a three-way analysis of variance, then a two-way analysis of variance was performed; and if the *F*-tests were significant in both analyses, a paired *t*-test was done. Differences were considered to be significant at the probability value of 0.05 or less. Halothane concentrations in blood were measured using a modification of the gas chromatographic method reported by Lowe (16).

Results

Halothane concentration in perfusing blood was measured in all six dogs in the severe hypoxia group and in three of five dogs in the moderate hypoxia group. Halothane concentrations at 15 min after exposure to 1% and to 2% halothane were 0.70 ± 0.05 ($n = 9$) and 1.52 ± 0.20 ($n = 6$) mM, respectively.

Table 1 shows the changes in hemoglobin, pH, P_{CO_2} , partial pressure of oxygen (P_{O_2}), and base excess measured immediately before exposure to hypoxia (baseline) and at 3 and 4 min of hypoxia in

Table 1. Changes in Blood Gases Caused by Severe and Moderate Hypoxia

	Hb (g/dL)		pH (U)		Po ₂ (mm Hg)		Pco ₂ (mm Hg)		BE (mEq/L)	
	Baseline	Hypoxia	Baseline	Hypoxia	Baseline	Hypoxia	Baseline	Hypoxia	Baseline	Hypoxia
Severe hypoxia (n = 6)										
Control	9.0 ± 0.7	9.2 ± 0.8	7.44 ± 0.04	7.44 ± 0.04	408.7 ± 23	19.3 ± 2.8 ^a	33.6 ± 2.2	31.1 ± 2.2	-1.1 ± 1.4	+0.5 ± 1.1
1% HAL	9.4 ± 1.0	9.2 ± 0.7	7.42 ± 0.02	7.47 ± 0.02	360.1 ± 7.7	18.8 ± 2.2 ^a	35.0 ± 2.1	31.0 ± 2.3	-1.8 ± 0.8	-0.3 ± 0.9 ^a
2% HAL	9.0 ± 0.6	9.1 ± 0.8	7.41 ± 0.03	7.47 ± 0.02	350.6 ± 18.6 ^b	19.3 ± 3.0 ^a	36.3 ± 1.7	31.3 ± 1.8	-1.7 ± 1.6	-0.1 ± 1.3 ^a
Moderate hypoxia (n = 5)										
Control	8.9 ± 0.4	8.6 ± 0.3	7.42 ± 0.04	7.44 ± 0.04	375.2 ± 27.8 ^a	46.8 ± 2.1 ^a	38.5 ± 2.9	36.8 ± 2.9	+0.6 ± 1.7	+0.5 ± 1.6
1% HAL	8.6 ± 0.4	9.0 ± 0.2	7.40 ± 0.05	7.42 ± 0.05	361.8 ± 21.6	50.4 ± 2.7 ^a	39.4 ± 3.3	36.4 ± 3.3	0.0 ± 1.8	-0.8 ± 1.5
1% HAL+DEN	9.0 ± 0.4	9.1 ± 0.4	7.43 ± 0.05	7.42 ± 0.06	336.5 ± 21.3 ^b	52.4 ± 3.1 ^a	35.1 ± 2.2	38.2 ± 3.1	+0.6 ± 2.8	-0.4 ± 2.1

HAL, halothane; DEN, chemoreceptor deafferentation; Hb, hemoglobin; Po₂, partial pressure of oxygen; Pco₂, partial pressure of carbon dioxide; BE, base excess.

^aP < 0.05 vs baseline.

^bP < 0.05 vs control.

Table 2. Baseline Values of Mean Arterial Pressure and Regional Outflows in Severe and Moderate Hypoxia Group

	MAP (mm Hg)	Outflow (mL·kg ⁻¹ ·min ⁻¹)		
		Splanchnic	Coronary	Other
Severe hypoxia (n = 6)				
Control	88 ± 3	74.0 ± 7.1	5.0 ± 0.9	51.4 ± 7.7
1% HAL	72 ± 3 ^a	69.7 ± 6.6	4.7 ± 0.8	54.4 ± 8.7
2% HAL	60 ± 3 ^{a,b}	68.7 ± 6.4 ^a	5.0 ± 0.9	54.9 ± 7.0
Moderate hypoxia (n = 5)				
Control	86 ± 7	56.7 ± 2.8	3.6 ± 0.6	44.9 ± 2.4
1% Hal	72 ± 5 ^a	56.2 ± 2.4	3.7 ± 0.9	45.7 ± 2.5
1% HAL+DEN	69 ± 4 ^a	52.5 ± 3.3	3.8 ± 0.8	49.3 ± 3.6

HAL, halothane; DEN, chemoreceptor deafferentation; MAP, mean arterial pressure.

^aP < 0.05 vs control.

^bP < 0.05 vs 1% halothane.

the severe and moderate hypoxia groups, respectively. There was no significant difference in the magnitude of hypoxia among the three conditions in each group. The values of Po₂ during hypoxia were 38.9 ± 1.7 (n = 11) and 22.8 ± 1.5 (n = 15) mm Hg at 1 and 2 min of severe hypoxia, respectively, and 109.3 ± 12.9 (n = 13), 67.7 ± 2.8 (n = 12), and 55.1 ± 2.2 (n = 13) mm Hg at 1, 2, and 3 min of moderate hypoxia, respectively.

Table 2 shows the baseline values (before hypoxia) of mean arterial pressure (MAP) and regional outflows. In the severe hypoxia group, halothane caused a dose-dependent decrease in MAP; in the moderate hypoxia group, 1% halothane reduced MAP but chemoreceptor deafferentation did not cause further change. Regional outflows were not altered by 1% halothane, 2% halothane, and 1% halothane with deafferentation except for the reduction in splanchnic outflow with 2% halothane in the severe hypoxia group.

The changes in MAP, venous outflows, and reser-

voir volumes during hypoxia are shown in Figure 2 (severe hypoxia) and Figure 3 (moderate hypoxia), MAP and each venous outflow being standardized to the baseline value and reservoir volume change. Mean arterial pressure increased above baseline values (time 0) in five of six dogs during severe hypoxia, but this increase was not statistically significant. Even during the presence of halothane, MAP did not change during severe hypoxia, but was significantly lower than in the control group (Figure 2). During moderate hypoxia, MAP showed a tendency to increase, but this increase was not significant. Mean arterial pressure decreased during 1% halothane and showed a further decrease when chemoreceptor deafferentation was added to 1% halothane (Figure 3). Severe hypoxia caused a profound decrease in splanchnic outflow (42% ± 4% baseline) and an increase in coronary (587% ± 118% baseline) and other (155% ± 11% baseline) outflow under control. Halothane attenuated these alterations in venous outflows but its effect on coronary outflow (Figure 2) was not considered significant because, in one case, coronary outflow increased during halothane administration. During moderate hypoxia, the changes in venous outflows were less than those during severe hypoxia. In splanchnic and other outflows, the changes were not significant at 4.5 min of moderate hypoxia. Coronary outflow increased to 199% ± 19% baseline during moderate hypoxia, although this increase was attenuated with 1% halothane (159% ± 13% baseline) and was further attenuated with deafferentation to 139% ± 14% baseline. However, this difference (halothane vs deafferentation) was not statistically significant (Figure 3). Reservoir volume increased by 22.3 ± 3.1 and 10.5 ± 1.6 mL/kg during severe and moderate hypoxia, respectively (Figures 2 and 3). Halothane attenuated this increase (Figures 2 and 3) and chemoreceptor deafferentation subsequent to 1% halothane completely abolished the

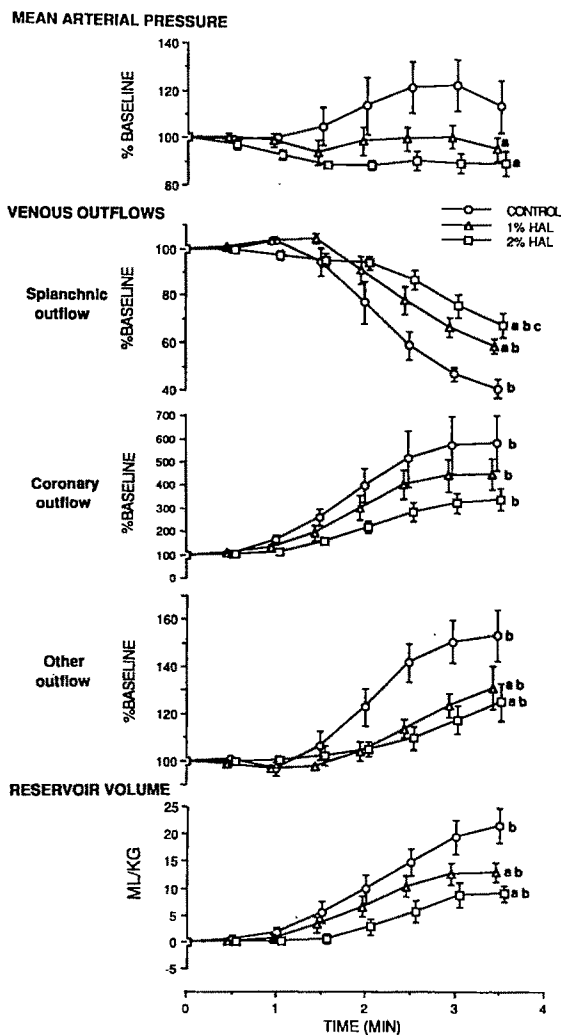


Figure 2. Time-course of changes after induction of severe hypoxia in MAP, venous outflow from three vascular beds, and reservoir volume during no halothane (control, circle), 1% halothane (triangle), and 2% halothane (square) anesthesia. HAL, halothane. ^a*P* < 0.05 vs control response. ^b*P* < 0.05 vs time 0. ^c*P* < 0.05 vs 1% halothane. (*n* = 6.)

increase and even elicited a reduction (-1.2 ± 0.5 mL/kg) in reservoir volume (Figure 3).

Figure 4 shows the hypoxia-induced changes in SENA standardized to the baseline level during control conditions. Complete recordings of nerve activity were accomplished in five of six dogs in the severe hypoxia group and five of five dogs in the moderate hypoxia group. Severe hypoxia provoked a large increase in SENA and no significant difference was seen among control, 1% halothane, and 2% halothane. During moderate hypoxia, SENA increased significantly from control and from the presence of 1% halothane. No change was seen during 1% halothane with deafferentation. Changes in coronary vascular resistance were calculated from the values of mean arterial pressure and coronary outflow. The

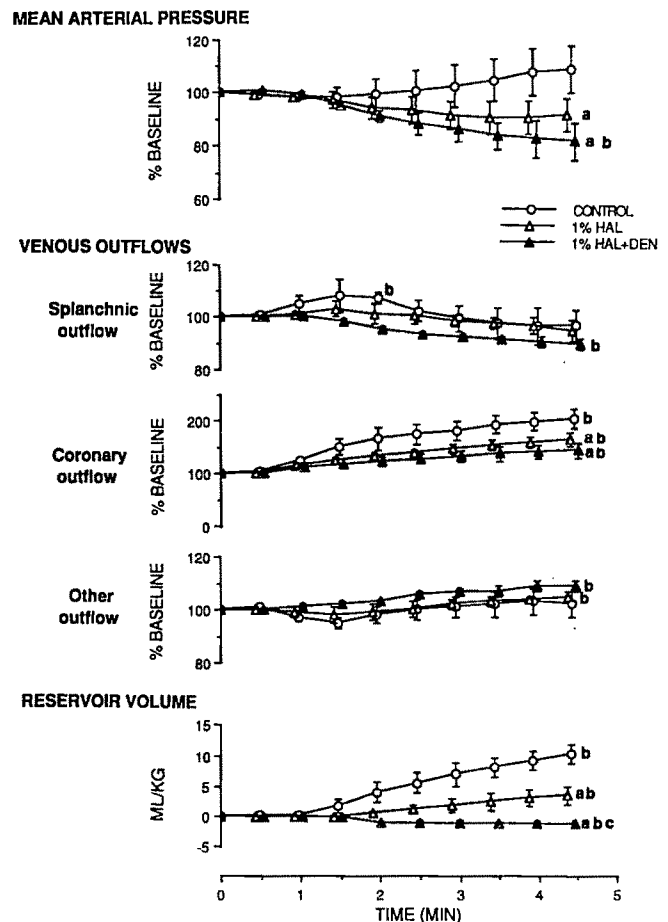


Figure 3. Time-course of changes after induction of moderate hypoxia in MAP, venous outflows from three vascular beds, and reservoir volume during control (no halothane, circle), 1% halothane (open triangle), and 1% halothane with chemoreceptor denervation (filled triangle). Note that the increase in reservoir volume was completely abolished after chemoreceptor denervation during 1% halothane. Statistical symbols are the same as in Figure 2.

time-course of coronary vascular resistance is shown in Figure 5. Two percent halothane reduced the baseline coronary resistance significantly. Severe hypoxia caused a profound reduction in coronary resistance, and the changes after 1 min of hypoxia during 1% halothane and 2% halothane were identical to those during control conditions. Moderate hypoxia also reduced coronary vascular resistance, but there was no significant difference among the three conditions: control, 1% halothane, and 1% halothane with deafferentation.

Discussion

The following principal results were obtained from this study. (a) Hypoxia tended to increase systemic vascular resistance and caused a decrease in systemic blood volume and total vascular capacitance depen-

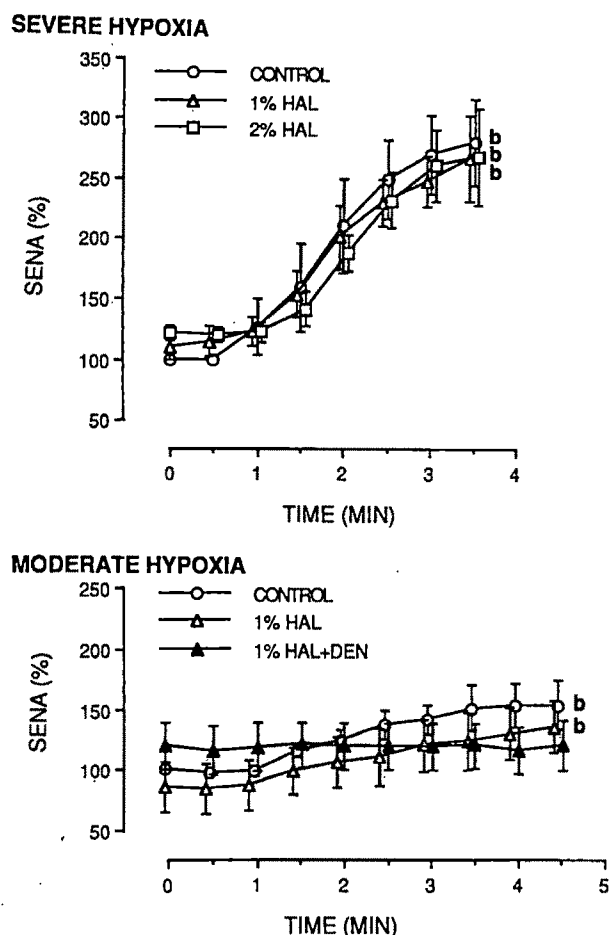


Figure 4. Changes in SENA in response to severe hypoxia (*top*, $n = 5$) under control (no halothane), 1% halothane, and 2% halothane and in response to moderate hypoxia (*bottom*, $n = 5$) under no halothane (control), 1% halothane, and with chemoreceptor denervation. Format is the same as in Figure 2.

dent on the severity of hypoxia. (b) Halothane attenuated the hypoxic vascular responses in both arterial and venous vascular beds but did not abolish the capacitance response completely. (c) Augmentation in sympathetic nerve activity in response to severe hypoxia was not attenuated by halothane. (d) Vascular responses to moderate hypoxia appear to be mediated entirely through peripheral chemoreceptors, and 1% halothane did not completely eliminate this chemoreceptor-mediated response. (e) The reduction in coronary resistance in response to hypoxia was dependent on arterial oxygen tension and not on the presence of halothane.

Systemic blood volume decreased by 10.5 and 22.4 mL/kg during moderate and severe hypoxia, respectively. This decrease in systemic blood volume can contribute to the increase in cardiac output that is observed during hypoxia (2,3) by increasing venous return to the heart. Rothe et al. (6) reported that severe hypoxia ($PO_2 = 35$ mm Hg) elicited an increase

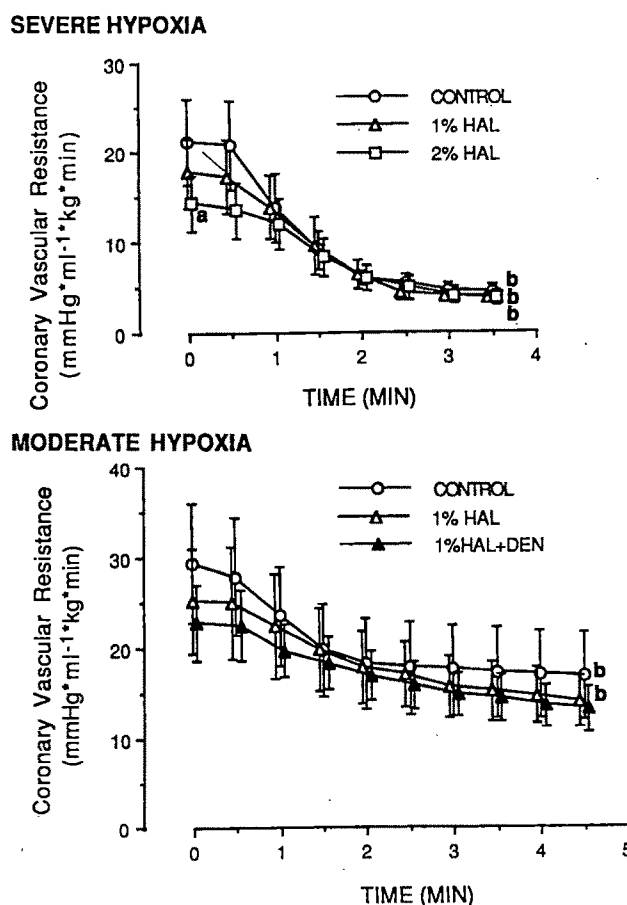


Figure 5. Time-course of coronary resistance in response to severe hypoxia (*top*, $n = 6$) and moderate hypoxia (*bottom*, $n = 5$). Format is the same as in Figure 2.

in mean circulatory filling pressure of 2.5 mm Hg, which is equivalent to a blood transfusion of 6.25 mL/kg (an amount less than our results). This dissimilarity in blood volume change might be due to differences in experimental method. Braunwald et al. (5), using cardiopulmonary bypass as employed in this study, reported that hypoxia (O_2 saturation = 50%) elicited a blood volume decrease of 16 mL/kg. Taking the magnitude of hypoxia into account, this value is quite consistent with our results. In our previous study (7), in which the experimental design was identical to that in our present study, active splenic contraction contributed to a total blood volume reduction of about 60% (14 mL/kg) during severe hypoxia ($PO_2 = 17$ mm Hg). This value of 14 mL/kg is close to the blood volume expelled from the spleen by supramaximal stimulation of the splenic nerve (9). These results suggest that the severe hypoxia used in our present study caused almost maximal sympathetic stimulation. They also suggest that hypoxia stimulates expulsion of blood from the systemic circulation in proportion to the severity of hypoxia that

began at a PO_2 level of about 70 mm Hg (at 2 min during moderate hypoxia) and that maximal blood volume contraction may be about 20 mL/kg at a PO_2 level of less than 20 mm Hg in dogs.

One of the circulatory adjustments during hypoxia in arterial vascular beds is the redistribution of blood flow because of uneven regional vascular resistance responses (14). Using microspheres in dogs, Adachi et al. (3) demonstrated that cardiac output increased and absolute blood flow increased to all organs except skin and muscle during hypoxia, although the fractional distribution of cardiac output decreased in the splanchnic bed and kidney. On the other hand, halothane itself has been reported to increase percent distribution of cardiac output to the brain, kidney, liver, and large intestine in rats (17) or to cause no profound redistribution (18) in rabbits using microspheres. In this study, we did not measure the inflow to each vascular bed. The baseline outflows, which were measured at steady-state conditions during control or during halothane administration (where the measured outflow can be considered to be equal to inflow if shunt flow is negligible) did not show a profound change. However, splanchnic outflow showed a small decrease, suggesting that halothane itself did not cause a profound flow redistribution during the conditions of the present study.

During severe hypoxia, marked decreases in splanchnic outflow and increases in coronary and other outflows were produced. Coronary outflow, which must be nearly equivalent to the inflow due to the small blood volume of the heart and short circuit time constant, increased about sixfold. This flow redistribution away from the splanchnic vascular bed, which has a long venous time constant, to coronary and other vascular beds, which have short time constants, results in an increase in venous return (11). Vascular capacitance cannot be solely the result of a passive change owing to flow distribution. Active change also contributes to a decrease in vascular capacitance, because an increase in sympathetic nerve activity caused by hypoxia can elicit venoconstriction and hence expel blood from the splanchnic vascular bed (16).

During hypoxia, an increase in coronary outflow, which indicates an increase in coronary inflow, was attenuated by halothane. However, the fact that hypoxic changes in coronary resistance were the same under control and under 1% and 2% halothane indicates that coronary resistance was controlled by the arterial PO_2 level and was not directly influenced by halothane. Therefore, the difference in coronary outflow among these three conditions must be due to alterations in perfusion pressure caused by halothane. This result is consistent with that reported by Vance et al. (19) demonstrating that a large increase

in coronary artery flow caused by hypoxia was not influenced by the presence of halothane. Although they reported that the hypoxic increase in coronary artery flow was not caused until PO_2 was less than 5.3 kPa, our study shows that the increase in coronary flow, or decrease in coronary resistance, can be elicited even during moderate hypoxia ($PO_2 = 50$ mm Hg).

The circulatory response to hypoxia was attenuated by halothane, but the augmentation of sympathetic nerve activity caused by severe hypoxia was not affected by halothane. Moderate hypoxia-induced sympathetic discharge during the presence of halothane tended to be lower than that under control. This discrepancy between the response in sympathetic discharge and vascular response during severe hypoxia suggests that the site of action of halothane in attenuating vascular responses to severe hypoxia is in the peripheral vessels rather than in the sympathetic nervous system. Skovsted et al. (20), experimenting on cats, reported a similar peripheral effect of halothane. They have demonstrated that halothane produced only a slight depression in sympathetic activity response to baroreceptor nerve stimulation, whereas the blood pressure response was markedly depressed (20). During hypoxia, the sympathetic discharge is stimulated through the chemoreceptor reflex and the so-called central pressor effect, which can be induced by extremely severe hypoxia and is augmented by decreased cerebral perfusion pressure (14). In a previous study, we found that even after chemoreceptor denervation, sympathetic nerve activity began to rise at 2.5 min of severe hypoxia, when the PO_2 was about 22 mm Hg (7).

These findings indicate that the augmentation of sympathetic nerve activity during moderate hypoxia is mediated almost entirely through peripheral chemoreceptors, whereas the late rise in sympathetic discharge after 2.5 min of severe hypoxia is the result of a combination of chemoreceptor stimulation and central pressor effect. Some investigators have shown that halothane depressed the response of peripheral chemoreceptors (13,21) but did not abolish that response even at 2% concentration (13). A decrease in systemic arterial pressure not only augments the chemoreceptor reflex through the interaction between arterial baroreceptor input and chemoreceptor input (14,22) but also augments the central pressor effect (14). Thus, halothane does not depress the response of sympathetic nerve activity to severe hypoxia. It is fully activated through chemoreceptor and central pressor effects, which are in turn augmented by halothane-induced hypotension. During moderate hypoxia, however, halothane appears to depress the response in sympathetic discharge, although the depression is not significant.

It should be noted that the dogs in this study were anesthetized with pentobarbital sodium. Although it has been reported that pentobarbital does not affect the chemosensory discharge (23), it may have contributed to the effect of halothane on hypoxic vascular responses when it was used in combination with halothane. Furthermore, as these experiments were done under constant perfusion flow using cardiopulmonary bypass, the role of cardiac performance should be taken into account as well.

In conclusion, halothane attenuates the hypoxic vascular response in both resistance and capacitance vessels, although it did not completely abolish the decrease in systemic blood volume. This attenuation plays an important role in masking the response of vital signs, especially arterial pressure, to hypoxia during halothane anesthesia. During severe hypoxia, augmentation in sympathetic nerve activity was not depressed by halothane; thus, the attenuation in vascular response must be due to the action of halothane at peripheral sites, possibly by changing the responsiveness of blood vessels to sympathetic stimulation or by inhibitory action at cardiac and vascular smooth muscle sites.

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Breathing Pattern and Occlusion Pressure Waveform in Humans Anesthetized With Halothane or Sevoflurane

Tetsuo Kochi, MD, Yoshiko Izumi, MD, Shiro Isono, MD, Toru Ide, MD, and Tadanobu Mizuguchi, MD

Department of Anesthesiology, Chiba University School of Medicine, Chiba, Japan

To examine the ventilatory effects of sevoflurane, breathing pattern, airway occlusion pressure waveform, and the mechanical variables of the respiratory system were determined in seven subjects anesthetized with sevoflurane and in an additional seven subjects anesthetized with halothane. All patients breathed 1 MAC of anesthetic using oxygen as the carrier gas, and the measurements were performed in the absence of surgical stimulation. The durations of inspiration and expiration were significantly longer during sevoflurane than during halothane administration. Tidal volumes were larger in the sevoflurane group than in the halothane group. Occlusion pressure waveforms were also markedly different between the two groups. Occlusion pressure during the

initial 300–400 ms tended to be less in the sevoflurane-anesthetized than in the halothane-anesthetized subjects. There was no evidence of an active Hering-Breuer reflex with either anesthetic. Mechanical variables of the respiratory system were essentially identical between the two anesthetics. We conclude that (a) the ventilatory effects of halothane and sevoflurane are different, (b) the difference in the respiratory timing and depth of breathing originates from the action of the anesthetics on the central respiratory neural network, and (c) the different shape of the tracheal occlusion pressure may be largely due to the different effects of halothane and sevoflurane on the muscles of the rib cage.

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The sensitivity to inhaled anesthetics may differ between diaphragm and other respiratory muscles. Tusiewicz et al. (1) have demonstrated that the inspiratory muscles of the rib cage in halothane-anesthetized humans are more vulnerable than the diaphragm is to the depressant effects of halothane. Under these circumstances, frank retraction of the rib cage appeared during early inspiration, indicating that the passive rib cage is not rigid enough to resist being sucked in by the decrease in pleural pressure generated by the diaphragm. Such a decrease in the stabilizing action of the intercostal muscles of the rib cage should also be related to the shape of the inspiratory driving pressure waveform. However, little attention has been paid to the waveform of the tracheal occlusion pressure in anesthetized human subjects, despite its obvious importance in determining both the form of the spirogram and hence the effects that changes in respiratory timing will have on ventilation.

Recent experiments performed in our laboratory revealed that inhaled anesthetics have varying effects on the diaphragmatic contractile function in vivo, namely enflurane depresses diaphragmatic function more than halothane does (2). Similar, although less marked, depression of diaphragmatic function was also observed in sevoflurane-anesthetized dogs (3). This difference in the direct effects of anesthetics on the diaphragm and, possibly, on the inspiratory intercostal muscles may also bring about a different shape of the tracheal occlusion pressure waveform.

Volatile anesthetics may also exert varying effects on the respiratory timing. For example, Marsh et al. (4) reported that, in dogs, duration of inspiration was longer during enflurane than during halothane anesthesia irrespective of the vagal input. Similar difference in respiratory timing was also observed in humans between enflurane and halothane anesthesia (5).

Thus, we hypothesized that halothane and sevoflurane act differently on the respiratory controlling mechanisms through their central and peripheral effects. We compared the patterns of breathing, shape of the occlusion pressure waveform, and the

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Address correspondence to Dr. Kochi, Department of Anesthesiology, Chiba University, School of Medicine, 1-8-1, Inohana, Chiba-shi, Chiba, 280 Japan.

Table 1. Anthropomorphic Data and Pulmonary Function Tests of Halothane and Sevoflurane Groups

	Age (yr)	Height (cm)	Weight (kg)	FVC (L)	FEV _{1.0} (L)
Halothane (n = 7)	44.9 ± 2.0	157.7 ± 2.0	51.1 ± 2.3	2.71 ± 0.25	2.26 ± 0.21
Sevoflurane (n = 7)	43.1 ± 4.6	156.5 ± 1.4	50.9 ± 1.8	2.64 ± 0.14	2.28 ± 0.15

FVC, forced vital capacity; FEV_{1.0}, forced expired volume in 1 s.
Values are mean ± SEM.

mechanical behavior of the respiratory system to investigate possible differences in the mode of action between halothane and sevoflurane. Recently developed noninvasive techniques for assessing the control and mechanics of breathing (6-8) were used.

Methods

The study was approved by the institutional ethical review committee and informed consent was obtained from all patients.

Fourteen patients scheduled for minor gynecologic surgery were allocated to receive halothane (n = 7) or sevoflurane (n = 7). The choice of anesthetic was decided by each anesthetist who was unaware of the purpose of the study. However, anesthetists responsible for the last three subjects were asked to administer halothane as the number of patients given halothane was only four after data had been collected from seven sevoflurane-anesthetized subjects. None had any significant cardiorespiratory or neuromuscular disorders. Patient characteristics and the results of preoperative pulmonary function tests are listed in Table 1. No preanesthetic medication was given before the induction of anesthesia. Anesthesia was induced with either halothane- or sevoflurane-nitrous oxide (66%)/oxygen via mask. After obtaining an adequate level of anesthesia, respiration was controlled manually and the nitrous oxide was discontinued. The trachea was intubated (inside diameter, 7.5 mm) without the aid of muscle relaxants. Spontaneous breathing was allowed to resume after tracheal intubation. Fractional concentrations of carbon dioxide and anesthetics were continuously monitored by an anesthetic/respiratory gas monitor (Albion Instruments, RASCAL). A minimum alveolar concentration of 1.0 of halothane and sevoflurane was defined as 0.74% and 1.71%, respectively (9). Tracheal pressure (Ptr) was measured using a differential pressure transducer (Nihon Koden, TP-603T) at the connection of the endotracheal tube and the flowmeter. Air flow (\dot{V}) was measured by a hot-wire flowmeter (Minato, RF-H) and changes in lung volume (ΔV) were obtained by electrical integration of

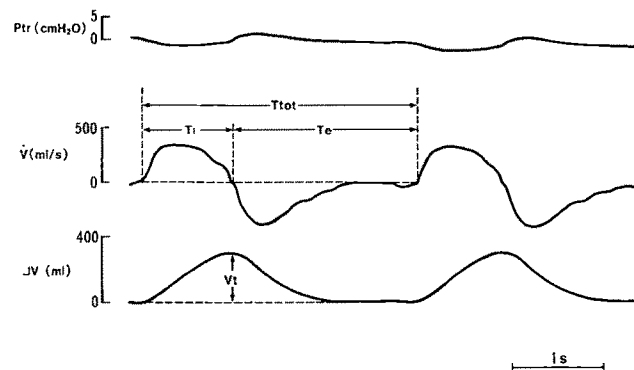


Figure 1. Tracing of tracheal pressure (Ptr), airflow (\dot{V}), and changes in lung volume (ΔV) in a subject anesthetized with sevoflurane. T_I , duration of inspiration; T_E , duration of expiration; T_{TOT} , respiratory cycle time; V_T , tidal volume.

the \dot{V} signal. Ptr, \dot{V} , and ΔV were recorded on a four-channel recorder. All measurements were performed at least 30 min after tracheal intubation and before the start of surgical procedures. In each subject, steady-state conditions (i.e., stable \dot{V} , ΔV , and end-tidal carbon dioxide concentration at end-tidal anesthetic concentration of 1 MAC for at least 10 min) were confirmed before starting the measurements. Ventilatory variables during unobstructed breathing were recorded for 2 min. Then, five end-inspiratory airway occlusions followed by five end-expiratory airway occlusions were performed every 10 breaths by turning the three-way stopcock incorporated into the breathing circuit. Durations of inspiration (T_I) and expiration (T_E) and the respiratory cycle time (T_{TOT}) were measured from the \dot{V} signal and tidal volume (V_T) was determined from the ΔV signal as shown in Figure 1. Using these variables, mean inspiratory flow rate (V_T/T_I), duty ratio (T_I/T_{TOT}), respiratory frequency (f), and minute ventilation (\dot{V}_E) were calculated.

Passive respiratory elastance (Ers) was calculated according to the following equation described by Zin et al. (8):

$$E_{rs} = P_{st,rs}/\Delta V, \quad (1)$$

where $P_{st,rs}$ is the static pressure of the respiratory system obtained during the end-inspiratory airway

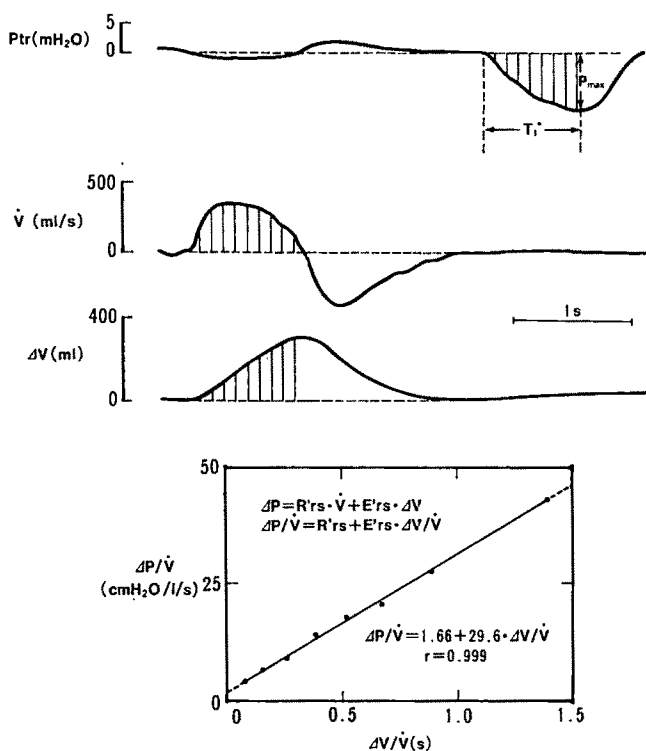


Figure 2. Tracing of tracheal pressure (P_{tr}), airflow (\dot{V}), and volume (ΔV) in a spontaneously breathing anesthetized subject. Occlusion of external airway was performed during expiration by turning the three-way stopcock incorporated into the breathing circuit and was maintained during an entire respiratory cycle. During this period, the inspiratory effort indicated by negative P_{tr} , was measured at 0.1-s intervals after onset of occluded inspiration. \dot{V} and ΔV of the preceding breath were measured in the same way.

occlusion and ΔV is the corresponding change in lung volume. Active respiratory elastance ($E'rs$) and resistance ($R'rs$) were also calculated by the method reported by Siafakas et al. (7), which is based on the following equation of motion:

$$-P^{o_{tr}} = R'rs \cdot \dot{V} + E'rs \cdot \Delta V, \quad (2)$$

where $P^{o_{tr}}$ is the tracheal pressure during an inspiratory effort with the airways occluded at functional residual capacity, representing the inspiratory driving pressure, and \dot{V} and ΔV are, respectively, the instantaneous flow and volume changes during a control breath immediately preceding the occluded effort (Figure 2). P_{tr} during airway occlusion was measured at 0.1-s intervals after onset of occluded inspiration. \dot{V} and ΔV of the preceding breath were measured in the same way, and data were plotted according to the following equation modified from Equation (2):

$$(-P^{o_{tr}} - K_1 \cdot \dot{V} - K_2 \cdot \dot{V}^2) / \dot{V} = R'rs + E'rs \cdot \Delta V / \dot{V}, \quad (3)$$

where K_1 and K_2 are constants representing the pressure-flow relationship of the endotracheal tube,

Table 2. Ventilatory Variables and Partial Arterial Pressure of Carbon Dioxide of Each Group

	Halothane (n = 7)	Sevoflurane (n = 7)	P
T_I (s)	0.86 ± 0.02	1.06 ± 0.05	<0.01
T_E (s)	1.27 ± 0.08	1.91 ± 0.26	<0.05
T_I/T_{TOT}	0.41 ± 0.01	0.37 ± 0.02	NS
f (beats/min)	28.5 ± 1.2	21.2 ± 1.7	<0.01
V_T (mL)	232 ± 31	274 ± 41	<0.05
V_T/T_I (mL/s)	268 ± 27	259 ± 17	NS
\dot{V}_E (L/min)	6.56 ± 0.29	5.72 ± 0.35	NS
P_{aCO_2} (mm Hg)	44.1 ± 2.3	45.5 ± 1.1	NS

T_I , duration of inspiration; T_E , duration of expiration; T_{TOT} , respiratory cycle time; T_I/T_{TOT} , duty ratio; f, frequency of breathing; V_T , tidal volume; V_T/T_I , mean inspiratory flow rate; \dot{V}_E , minute ventilation; P_{aCO_2} , arterial carbon dioxide tension.

Values are mean \pm SEM.

hot-wire flowmeter, and connectors. The pressure-flow characteristics of the equipment used in the study were determined in vitro by measuring the pressure difference across the equipment while blowing 100% oxygen at various flow rates (0–10 L/s). This was curvilinear, fitting Rohrer's equation ($P = K_1 \dot{V} + K_2 \dot{V}^2$). The values of K_1 and K_2 amounted to 3.4 and 7.7, respectively. Equation (3) was obtained by subtracting from $-P^{o_{tr}}$ in Equation (2) the resistive pressure drop due to the equipment (including the endotracheal tube) and dividing both sides of the equation by \dot{V} . Equation (3) is a linear function of the general type $y = a + bx$, where $E'rs$ is the slope and $R'rs$ is the intercept on the y-axis. Linear relationships were obtained in all subjects, with correlation coefficients (r) greater than 0.99.

An arterial blood sample was drawn at the end of the experimental procedures and the partial pressure of carbon dioxide (P_{aCO_2}) was measured using the blood gas analyzer (Radiometer, ABL2). Results were analyzed using the least-squares regression analysis and Student's *t*-test where appropriate. Statistical differences were considered significant at $P < 0.05$.

Results

Ventilatory variables and the value of P_{aCO_2} obtained in each group are shown in Table 2. The administration of sevoflurane was associated with significantly longer inspiratory and expiratory times than administration with halothane was, whereas duty ratio was the same between the groups. Although tidal volumes were significantly larger in the patients given sevoflurane, reflecting the decrease in breathing frequency, minute ventilation and P_{aCO_2} were not different between the two groups. Mean inspiratory flow rate, calculated as tidal volume/inspiratory du-

Table 3. Individual Values of T_r^o/T_i , P_{\max}/T_r^o and $P_{0.1}$ of Halothane- and Sevoflurane-Anesthetized Subjects

Subject No.	Halothane group			Sevoflurane group		
	T_r^o/T_i	P_{\max}/T_r^o (cm H ₂ O/s)	$P_{0.1}$ (cm H ₂ O)	T_r^o/T_i	P_{\max}/T_r^o (cm H ₂ O/s)	$P_{0.1}$ (cm H ₂ O)
1	0.85	8.23	2.18	0.81	8.40	0.63
2	0.81	10.00	1.89	0.98	10.95	1.51
3	0.83	10.59	1.81	0.90	9.82	1.36
4	0.82	11.04	2.86	0.90	10.94	1.31
5	0.83	11.25	2.83	0.99	9.22	1.89
6	0.80	8.26	2.13	0.89	9.99	1.38
7	0.81	9.62	2.81	0.87	10.57	0.60
Mean	0.82	9.86	2.36	0.90	9.98	1.24 ^a
SEM	0.01	0.47	0.17	0.02	0.36	0.18

T_r^o/T_i , ratio of occluded inspiratory time and the unoccluded inspiratory time; P_{\max}/T_r^o , overall slope of the occlusion pressure waveform; $P_{0.1}$, occlusion pressure at 0.1 s after the inspiratory effort.

^aSignificant difference as compared with the value for the halothane group; $P < 0.05$.

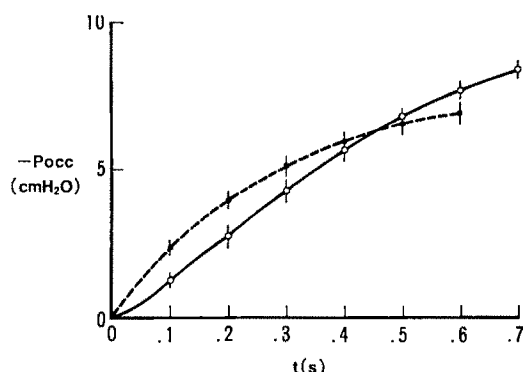


Figure 3. Occlusion pressure waveforms of halothane- and sevoflurane-anesthetized subjects. Pressure was measured in 100-ms intervals and averaged for seven subjects in each group. Values are mean \pm SEM. ●, halothane; ○, sevoflurane.

ration (V_T/T_i), was similar in the two groups (Table 2).

In both groups, the ratios of occluded inspiratory time and the unoccluded inspiratory time (T_r^o/T_i) were less than 1, indicating that the duration of inspiration was decreased by airway occlusion (Table 3). The overall slopes of the occlusion pressure waveform (P_{\max}/T_r^o) were not statistically different between halothane- and sevoflurane-anesthetized subjects. In contrast to the similarity of P_{\max}/T_r^o between the two groups, occlusion pressure at 0.1 s after the inspiratory effort was significantly less in the subjects who received sevoflurane than in those given halothane. Furthermore, as shown in Figure 3, occlusion pressure waveforms were also markedly different between the two groups. Occlusion pressure waveforms of all halothane-anesthetized subjects and two sevoflurane-anesthetized subjects were convex upward, whereas the remaining five subjects anesthetized with sevoflurane exhibited a more complex pattern (i.e., concave upward during the early

Table 4. Average Values of Passive Respiratory Elastance, Active Respiratory Elastance, and Active Respiratory Resistance of Halothane and Sevoflurane Groups

	Ers (cm H ₂ O/L)	E'rs (cm H ₂ O/L)	R'rs (cm H ₂ O·L ⁻¹ ·s ⁻¹)
Halothane (n = 7)	22.3 \pm 2.8	28.0 \pm 3.0	2.42 \pm 0.64
Sevoflurane (n = 7)	21.8 \pm 0.9	28.7 \pm 1.7	3.21 \pm 0.63

Ers, passive respiratory elastance; E'rs, active respiratory elastance; R'rs, active respiratory resistance.

Values are mean \pm SEM.

inspiration and convex upward during the late inspiratory phase).

Ers, E'rs, and R'rs were identical between the subjects anesthetized with halothane and those anesthetized with sevoflurane, indicating that the two anesthetics exert an essentially similar effect on the mechanical behavior of the respiratory system (Table 4). In agreement with the previous observations (5), the values of E'rs were greater than those of Ers ($P < 0.01$, paired t -test) in all subjects.

Discussion

The main findings of this study are that, at anesthetic depth of 1 MAC, halothane and sevoflurane exert a similar degree of ventilatory depression as assessed by \dot{V}_E and P_{aCO_2} . Also, mechanical variables of the respiratory system are identical between halothane- and sevoflurane-anesthetized patients, whereas effects on the respiratory timing and depth of breathing are different between the anesthetics. In addition, the shape of the tracheal occlusion pressure waveform is markedly different between the two groups of patients.

Respiratory Timing

We found no significant difference in V_T/T_I , \dot{V}_E , and $Paco_2$ between halothane and sevoflurane at 1 MAC of anesthesia. Thus, the degree of ventilatory depression exerted by these two anesthetics is comparable at least at 1 MAC. However, the patterns of breathing determined in terms of T_I , T_E , and V_T were significantly different between the two groups. The difference of the respiratory timing between the anesthetics may be due to the different degree of the strength of the Hering-Breuer inflation reflex (10). However, the reflex is probably not operative at the normal range of tidal volume in humans (11). Furthermore, duration of occluded inspiration (T_I^o) is equal to, or slightly shorter than, the duration of unoccluded inspiration (T_I) not only during halothane but also during enflurane anesthesia (5), indicating that the Hering-Breuer inflation reflex does not regulate respiratory timing during halothane or enflurane anesthesia. This is also the case in our study where average values of T_I and T_I^o in patients anesthetized with halothane were 0.86 ± 0.02 and 0.73 ± 0.15 s, respectively ($P < 0.05$), whereas those of sevoflurane amounted to 1.06 ± 0.13 and 0.98 ± 0.09 s (mean \pm SD), respectively ($P < 0.05$).

The mechanical behavior of the respiratory system is another important determinant of the breathing pattern. For example, an alteration of elastic and/or resistive component of the respiratory system may change the pattern of breathing through its effects on the load compensatory mechanisms (12). Concerning this point, our values of passive and active elastance in patients anesthetized with halothane are not different from those in patients anesthetized with sevoflurane. Active respiratory resistance in subjects breathing halothane is also comparable to that in subjects given sevoflurane. Furthermore, these values are in agreement with those determined in previous studies of patients anesthetized with halothane (6).

Considering the absence of the Hering-Breuer inflation reflex and the lack of a significant difference in mechanical behavior of the respiratory system between the anesthetics, the most likely explanation for the different respiratory patterns is that each anesthetic affects central respiratory regulatory mechanisms differently. In this regard, Marsh et al. (4) have reported a similar difference in respiratory timing and depth of breathing in dogs anesthetized with halothane or enflurane and concluded that the difference originates from the different effect of the two anesthetics on the bulbopontine "pacemaker" mechanism. Besides, Gautier et al. (13) have shown that increasing respiratory frequency induced by halothane can be abolished by midcollicular decerebration, indicating that the tachypneic properties of

halothane stem from the effect of the anesthetic on the suprapontine structures.

Respiratory Drive

In general, V_T/T_I reflects the central respiratory drive (14). V_T/T_I , on the other hand, can be affected by the inspiratory flow profile. When the inspiratory volume-time profile is not linear, V_T/T_I is no longer a pure index of inspiratory drive because it is time-dependent (15). In this regard, the analysis of the tracheal occlusion pressure waveform provides useful information as it is the driving pressure potentially available during inspiration.

Our results demonstrate that occlusion pressure at 0.1 s was significantly less in sevoflurane-anesthetized patients than in those anesthetized with halothane. Moreover, as illustrated in Figure 3, the occlusion pressure waveform was also markedly different between the two groups of patients. It is noteworthy that Marsh and colleagues (4) have also noticed similar differences in the shape of the occlusion pressure waveform between halothane and enflurane anesthesia in dogs. However, the mechanisms responsible for the period of low negative pressure during early inspiration during enflurane anesthesia was unclear. The shape of the occlusion pressure waveform has been shown to reflect the shape of the inspiratory neural drive (7,14). Consequently, a change in occlusion pressure is usually considered to indicate an alteration in respiratory drive. But other explanations exist: (a) changes in functional residual capacity and in the configuration of the chest wall, (b) neuromuscular blocking action and/or the effects on the excitation contraction coupling process in the respiratory muscles, and (c) changes in the pattern of contraction among various respiratory muscles. All these factors can influence the transformation of central respiratory drive into occlusion pressure.

In this regard, changes in functional residual capacity occur immediately after induction of anesthesia and do not change further with increasing depth of anesthesia or with administration of muscle relaxant (16,17). Thus, although we did not measure functional residual capacity in our subjects, it would be reasonable to assume that the two anesthetics produced similar decreases in lung volume. Alteration of neuromuscular transmission and/or the contractility of the respiratory muscles may have influenced the relation between the occlusion pressure and the central neural drive. In fact, we have shown that the transdiaphragmatic pressure during bilateral phrenic nerve stimulation in sevoflurane-anesthetized dogs was less than that found in halothane-anesthetized dogs at comparable anesthetic depth.

(2,3). If these results can be applied to human subjects and to other respiratory muscles, lower occlusion pressure during early inspiration in sevoflurane-anesthetized patients would be reasonably supported.

Jones et al. (18) and Tusiewicz et al. (1) have demonstrated that the relative contribution of the rib cage to tidal volume is reduced with halothane anesthesia. This reduction is associated with disappearance of the phasic activity of the parasternal inspiratory intercostal muscles (1) which, in turn, impairs stabilization of the rib cage. Reduced intercostal muscle tone, or a delay of the intercostal muscle contraction beyond the time when diaphragmatic descent has begun, may result in paradoxical rib cage motion and reduced $P_{0.1}$. If such depression of intercostal muscle function is greater during sevoflurane anesthesia than during halothane anesthesia, a greater disturbance of the coordinated motion of the chest wall and consequently lower occlusion pressure would result during early inspiration in sevoflurane-anesthetized subjects. Thus, we suggest that the different patterns of occlusion pressure waveform may be largely due to the different effects of halothane and sevoflurane on the muscles of the rib cage.

In conclusion, we suggest that the difference in the respiratory timing and depth of breathing between halothane- and sevoflurane-anesthetized patients originates primarily from the different effects of the two anesthetics on the central respiratory neural network. In addition, the different shape of the tracheal occlusion pressure waveform may be due largely to the different effects of halothane and sevoflurane on the muscles of the rib cage. Whether this differential effect involves neural (different degree of sensitivities of the phrenic and intercostal motoneuron pools) or muscular (different action of the anesthetics on the neuromuscular transmission and/or contractile properties of the respiratory muscle itself) mechanism remains to be elucidated in humans.

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Reliability of Capnography in Identifying Esophageal Intubation With Carbonated Beverage or Antacid in the Stomach

Sam T. Sum Ping, MB ChB, FFARCS, Mahesh P. Mehta, MD, and Tommy Symreng, MD, PhD
University of Iowa, College of Medicine, Iowa City, Iowa

To evaluate the reliability of capnography in identifying esophageal intubation in the presence of a carbonated beverage in the stomach, we first investigated the amount of CO₂ released from different carbonated beverages and antacids in a simulated stomach; next we measured the end-expired CO₂ level during esophageal ventilation with a carbonated beverage in the stomachs of six swine. CO₂ levels of approximately 20% were consistently observed in all carbonated beverages. The CO₂ levels obtained with sodium bicarbonate, Maalox, and so-

dium citrate were 19.3%, 2.0%, and 0%, respectively. CO₂ waveforms were observed during esophageal ventilation in five of six animals after intragastric administration of a carbonated beverage. An end-expired CO₂ level of 2.5% or more was observed in two swine. The highest end-expired CO₂ level measured was 5.3%. We conclude that although capnography is convenient and effective, it lacks all the attributes of an ideal monitor for detecting esophageal intubation.

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Capnography is an effective and popular method for identifying correct placement of endotracheal tubes (1,2). There is, however, evidence that carbon dioxide (CO₂) waveforms similar to those observed with tracheal intubation can be obtained with esophageal ventilation (3,4) with an end-expired CO₂ level as high as 2.0%. A normal CO₂ pattern during esophageal intubation has also been reported after ingestion of a carbonated beverage (5,6). Because these beverages are consumed so frequently in the United States, it is not uncommon for patients requiring emergency surgery to have recently drunk such a beverage. Another group of antacid-type beverages is also frequently ingested as medication for dyspepsia. One ingredient found in many antacids is sodium bicarbonate, which reacts with hydrochloric acid in the stomach to produce CO₂. If normal CO₂ levels and waveforms can be obtained during esophageal ventilation after ingestion of carbonated beverages or antacids, care must be exercised, at least during the first few ventilations,

before relying totally on capnography for correct placement of the endotracheal tube.

This study was designed to investigate the amount of CO₂ released from different carbonated beverages and antacids in a simulated stomach and the level of end-expired CO₂ obtained during esophageal ventilations after administration of carbonated beverages in the stomachs of swine.

Methods

Measurement of CO₂ Released From Carbonated Beverages and Antacids in a Simulated Stomach

Eight hundred milliliters of ambient air and 25 mL of 1 N hydrochloric acid (HCl), together with the contents of a freshly opened can of carbonated beverage (355 mL) at 2°C, were introduced into a 3-L rubber breathing bag. The latter was sealed and placed in a 38°C water bath. The CO₂ concentration of the gas in the bag was measured with a previously calibrated CO₂ infrared monitor (Beckman LBII). The pH and partial pressure of CO₂ (Pco₂) of the liquid in the bag were measured with a blood gas machine (IL 813 pH/blood gas analyser, Instrumentation Laboratory, Lexington, Mass.) at 1, 3, 5, and 10 min. The IL 813 machine does not measure pH lower than 3.3 or Pco₂ higher than 405 mm Hg. The carbonated beverages

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Address correspondence to Dr. Sum Ping, Department of Anesthesia, University of Iowa, College of Medicine, Iowa City, IA 52242.

studied were Diet Coke, Classic Coke, Pepsi, Diet 7-Up, and La Croix water. The procedure was done twice with Classic Coke and La Croix water, the second time with the omission of HCl.

The antacids used were 3 g (0.5 teaspoon) of sodium bicarbonate, 10 mL of Maalox (1.2 g of aluminum hydroxide and 0.6 g of magnesium hydroxide), and 30 mL of 0.3 M sodium citrate, each diluted with 150 mL of water for the study.

Measurement of End-Expired CO₂ With Esophageal Ventilation Before and After Administration of Carbonated Beverages in the Stomach of Swine

Six Yorkshire swine were studied with approval of the institutional animal investigation committee. After induction of anesthesia with intramuscular administration of 15–20 mg/kg of ketamine, a 7-mm cuffed endotracheal tube was placed through a tracheostomy. Anesthesia was maintained with 20 mg·kg⁻¹·h⁻¹ of intravenous pentobarbital and mechanical ventilation was performed through the tracheal tube with a tidal volume of 15 mL/kg (30% oxygen in nitrogen) at a rate to maintain normocarbida. Monitoring included electrocardiogram, mean systemic arterial blood pressure measurement with a catheter placed in the carotid artery, and a continuous recording of expired CO₂ waveforms (Beckman LBII interfaced with Linear 1200 penwriter). When stable conditions were established, another 7-mm cuffed tube, similar to the one in the trachea, was placed into the esophagus through the snout. The ventilator was connected to the latter tube and six ventilations were delivered to the esophagus. The ventilator was switched back to the tracheal tube, and the stomach was suctioned with a gastric tube passed through the esophageal tube. One hundred fifty milliliters (approximately half a can) of Diet Coke at 2°C was then instilled into the stomach through the gastric tube. The latter was removed and six more esophageal ventilations were delivered before reconnecting the ventilator to the tracheal tube. The stomach was again suctioned and the esophageal tube was removed.

Results

Carbon dioxide concentrations observed with the different beverages and antacids in the simulated stomach are shown in Table 1. The concentration of CO₂ in the simulated stomach increased over time with a maximum recorded at 10 min. A CO₂ concentration of approximately 20% was obtained after 10 min with all the carbonated beverages. Maximum CO₂ levels with sodium bicarbonate (3 g), Maalox (10 mL), and 0.3 M sodium citrate (30 mL) were 19.3%, 2.0%, and 0%, respectively.

Table 1. CO₂ Concentration at 1, 3, 5, and 10 min After Addition of Carbonated Beverage or Antacid With 25 mL of 1 N Hydrochloric Acid (HCl) and Without HCl in the Simulated Stomach

	CO ₂ concentration (%)			
	1 Min	3 Min	5 Min	10 Min
HCl present				
Diet 7-Up (355 mL)	15.2	18.0	19.8	21.7
Pepsi (355 mL)	6.4	11.2	14.5	17.9
Classic Coke (355 mL)	8.3	15.4	17.0	19.5
Diet Coke (355 mL)	8.5	14.4	17.7	20.6
La Croix (355 mL)	11.1	16.2	19.0	21.5
Maalox (10 mL)	1.2	1.5	1.7	2.0
NaHCO ₃ (3 g)	15.9	18.2	18.9	19.3
0.3 M sodium citrate (30 mL)	0	0	0	0
No HCl present				
Classic Coke (355 mL)	14.3	17.1	19.0	20.8
La Croix (355 mL)	11.0	15.2	17.8	20.5

The partial pressure of CO₂ and pH measured with all the carbonated beverages, except La Croix water, were ≥405 mm Hg and ≤3.3, respectively. The pH of La Croix water was 4.9; after addition of HCl, pH was ≤3.3. The partial pressure of CO₂ on both occasions was ≥405 mm Hg. The pH with the sodium bicarbonate, Maalox, and sodium citrate mixtures was 6.3, 4.0, and 3.3, respectively.

End-expired CO₂ levels during the first six esophageal ventilations in the animal model before and after instillation of carbonated beverage are shown in Table 2. The highest end-expired CO₂ measured was 5.3% when carbonated beverage was present in the stomach (Figure 1b). The CO₂ level in the same animal was 0.4%–0.5% with esophageal ventilations before addition of carbonated beverage (Figure 1a).

CO₂ waveforms were observed in five of six animals during esophageal ventilations both before and after addition of carbonated beverage. End-expired CO₂ levels of ≥2.5% were seen in two animals after administration of carbonated beverage (Table 3).

Table 2. End-Expired CO₂ in Six Animals During Mechanical Ventilation

Ventilation	End-expired CO ₂ (%)		
	Tracheal	Esophageal	Esophageal after Cola
1st	4.8 ± 0.9	0.4 ± 0.3	2.0 ± 2.1
2nd	4.8 ± 0.9	0.3 ± 0.3	1.5 ± 1.9
3rd	4.8 ± 0.9	0.4 ± 0.3	1.3 ± 1.5
4th	4.8 ± 0.9	0.3 ± 0.2	1.1 ± 1.3
5th	4.8 ± 0.9	0.3 ± 0.2	1.1 ± 1.4
6th	4.9 ± 0.9	0.2 ± 0.1	1.4 ± 1.3

Values are mean ± SD.

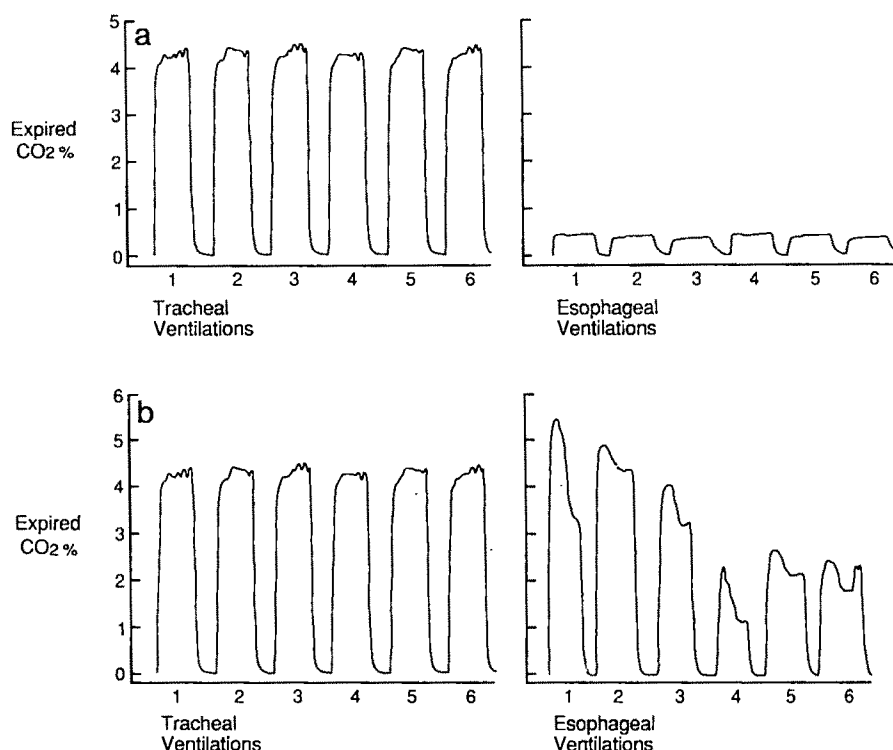


Figure 1. Expired CO₂ waveforms during tracheal and esophageal ventilations before (a) and after (b) addition of a carbonated beverage in the stomach.

Table 3. End-Expired CO₂ in Each Animal During Esophageal Ventilation With a Carbonated Beverage in the Stomach

Animal	End-expired CO ₂ (%) during esophageal ventilation					
	1st	2nd	3rd	4th	5th	6th
1	2.5	2.5	2.0	1.8	2.0	1.8
2	5.3	4.8	4.0	3.3	3.6	3.4
3	0.1	0.2	0.3	0.2	0.1	0.1
4	0	0	0	0	0	0
5	1.9	1.3	1.2	1.1	0.9	0.8
6	0	0	0.2	0.3	0.6	1.0

Discussion

An ideal monitor should exhibit a quick response time and have no false-positives or false-negatives. Unidentified esophageal intubation, although infrequent, always results in disaster; and any monitor on which total reliance is to be placed to identify esophageal placement of endotracheal tubes should be no less than ideal. Correct placement of endotracheal tubes can be confirmed by visualizing the presence of the endotracheal tube between the two vocal cords with laryngoscopy or by identifying tracheal rings and/or carina with bronchoscopy. Whether this degree of certainty could be exercised with capnogra-

phy for identifying esophageal intubation when the larynx cannot be visualized must be addressed.

This study showed that end-expired CO₂ levels usually seen with tracheal ventilation can also be observed with esophageal ventilations after ingestion of carbonated beverage, confirming previous reports (5). In a previous study (3), the decrease in end-expired CO₂ level with esophageal ventilation did not always follow a washout curve pattern as suggested by Salzarulo et al. (8). CO₂ waveforms should be observed at least beyond the sixth ventilation before an opinion is reached about placement of an endotracheal tube (7). In a worst-case scenario, when the vocal cords of an obese patient cannot be visualized, for example, correct placement of the endotracheal tube cannot be confirmed for at least another five ventilations, even if a normal-looking CO₂ waveform is observed during the first ventilation. The obese patient presents several additional problems: auscultation for breath sounds is more difficult, chest expansion on inspiration is not easily observed, and oxygen saturation decreases rapidly on apnea and on induction of anesthesia. Assuming a 700-mL tidal volume, a 9-L/min fresh gas flow rate into the circle system, and a minimal return of gas on expiration as is the case in esophageal ventilation (3), delivery of six ventilations normally takes 30 s. This long wait is unacceptable especially with a rapidly decreasing

arterial oxygen saturation. Following the oxygen saturation trend with a pulse oximeter may not help in distinguishing esophageal from tracheal intubation because there is usually a delay between ventilation of the lung with 100% oxygen and improvement in oxygen saturation.

CO₂ waveforms with esophageal ventilations were recorded immediately after the instillation of carbonated beverage (Diet Coke) into the stomach. The concentration of CO₂ in the stomach depends on the rate of CO₂ production and excretion. CO₂ is released into the stomach from the carbonic acid in the beverage whenever CO₂ concentration in the stomach reaches a point below that of the carbonic acid and CO₂ release continues until exhaustion of the carbonic acid. Excretion of CO₂ from the stomach is by passive absorption through the mucosa into the blood circulating through the capillaries of the stomach until CO₂ concentration in the stomach decreases to the level present in the blood. A larger volume of carbonated beverage ingested will maintain a high CO₂ concentration for a longer time. How CO₂ waveforms would be altered in relation to the time of administration of a specific volume of carbonated beverage during esophageal ventilations was not addressed in this study.

The 20% CO₂ concentrations observed with the carbonated beverages and sodium bicarbonate in the simulated stomach were unexpectedly high. The pattern of increasing CO₂ levels was probably due to the dynamics of the diffusion process of CO₂ released from the liquid. CO₂ concentration was highest above the liquid surface, and as there was no "movement en masse" like during expiration from the lung, diffusion was the major process for CO₂ to reach the sampling port. The increasing temperature of the liquid in the bag with heat transfer from the water bath also partly explains the increasing CO₂ concentration over time. An arbitrary volume of 800 mL of ambient air was added to simulate the gas bubble in the stomach. The normal volume of a stomach gas bubble is smaller and probably in the range of 50-200 mL. Higher CO₂ concentrations would have been observed under similar conditions with a smaller volume of gastric air.

Based on CO₂ concentrations observed in the simulated stomach, a higher CO₂ level should have been measured during esophageal ventilation after the addition of carbonated beverage. The highest CO₂ concentration recorded was 5.3%, much lower than the CO₂ level in the simulated stomach. This discrepancy can be explained by the following. The gastroesophageal sphincter allows gas to enter the stomach during "esophageal inspiration," whereas during "esophageal expiration" return of gas to the esophagus from the stomach depends on the degree of

competence of the gastroesophageal sphincter. No gas flows back through a competent sphincter during "expiration" and a CO₂ waveform will not be observed. An incompetent sphincter permits return of gas during "expiration," and the end-expired CO₂ level depends on the extent the stomach gas gets diluted by the incoming tidal volume.

The enthusiasm for using capnography to identify proper placement of endotracheal tubes has relied on the fact that CO₂ can only be produced in the lung. The two reported cases of esophageal ventilation with normal CO₂ pattern (4,5) were somewhat ignored because it was thought that the endotracheal tubes were in the trachea when the CO₂ waveforms were observed and slipped into the esophagus when laryngoscopy was performed (8). In our previous study, in which ventilation was administered in succession to two tubes (one in the trachea and one in the esophagus), we reported that CO₂ waveforms were observed in 33% of esophageal intubation (3). The highest level of CO₂ observed was 2%, and it may be argued that an end-expired CO₂ level of 2% will never be obtained with a properly placed endotracheal tube. However, with a carbonated beverage in the stomach, an end-expired CO₂ level as high as 5.3% can be observed with esophageal ventilation, and correct assessment of endotracheal tube placement becomes more difficult. The other limitation of capnography is that during cardiopulmonary resuscitation, when CO₂ excretion may be low or none (9), presence or absence of CO₂ waveforms does not help in determining correct placement of endotracheal tubes.

Esophageal ventilation may produce CO₂ waveforms with normal CO₂ concentration but abnormal shape, among other possible combinations. The abnormal CO₂ waveforms displayed by capnography may be an important clue in the early detection of esophageal intubation, whereas one would have been deceived by the normal CO₂ level indicated by the capnometer. Nevertheless, it should be remembered that the observation of normal CO₂ waveforms during the initial few ventilations is no guarantee of correct placement of the endotracheal tube (3,4).

Unidentified esophageal intubation is an avoidable cause of morbidity and mortality, and although capnography has made a major improvement in the accuracy of assessing correct placement of endotracheal tubes, it is not the perfect monitor. The search for the foolproof monitor must continue and, until then, anesthesiologists are strongly urged to use a capnograph instead of a capnometer and to continue observing the CO₂ waveforms for at least 1 min after placement of an endotracheal tube.

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Reflection of CO₂ Laser Radiation From Laser-Resistant Endotracheal Tubes

Mitchel Sosis, MD, PhD and Francis Dillon, MD

Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois; Department of Anesthesia, Indiana University School of Medicine, Indianapolis, Indiana

To assess the possibility of indirect damage by CO₂ laser reflection from specialized or modified tracheal tubes, four different tracheal tubes were studied. They were (1) a Rusch red rubber tracheal tube wrapped with 3M No. 425 aluminum foil tape, (2) a Rusch red rubber tracheal tube wrapped with Venture copper foil tape, (3) a polyvinylchloride tracheal tube wrapped with Laser-Guard protective coating, and (4) a Mallinckrodt Laser-Flex tracheal tube. The tracheal tubes were straightened and centered within cardboard cylinders and the laser set to 40 W was aimed to reflect from the tracheal tubes onto the cardboard. The times to combustion perforating the

cardboard cylinders because of laser reflection were 1.41 ± 0.54 (mean \pm sd), 1.73 ± 0.93 , 3.70 ± 2.18 , and 9.26 ± 3.40 s for tracheal tubes 1, 2, 3, and 4, respectively. The differences between the times to combustion with tracheal tubes 3 and 1, 3 and 2, 4 and 1, 4 and 2, and finally, 4 and 3 were statistically significant. We conclude that the Laser-Guard-wrapped polyvinylchloride tracheal tube and the Mallinckrodt Laser-Flex tracheal tube were less reflective of incident CO₂ laser radiation than the copper- or aluminum-foil-wrapped red rubber tracheal tubes.

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Accidental contact of CO₂ laser radiation with a combustible tracheal tube during laser airway surgery can convert the tracheal tube into a veritable "blowtorch" and cause extensive patient burns (1,2). In an effort to prevent laser-induced endotracheal tube fires, foil-wrapped rubber or polyvinylchloride or specially manufactured metallic endotracheal tubes have been advocated (3,4). However, these tubes may reflect the incident laser radiation with potential risk to the patient and operating room personnel. We sought to determine the possibility of indirect damage by CO₂ laser radiation reflected from either a specialized metallic endotracheal tube or from metal foil coverings used to protect conventional flammable endotracheal tubes.

Methods

A LaserSonics (Santa Clara, Calif.) model LS880 CO₂ laser in the continuous mode of operation was used with a Zeiss (Jena, Germany) Universal S2 operating microscope and 400-mm objective lens. The laser's

output was adjusted to 40 W with a 0.68-mm spot diameter. This power level is probably above that generally used clinically so that laser reflection occurring in practice may be of lesser intensity. Four different endotracheal tubes were evaluated: Rusch (Waiblingen, Germany) red rubber endotracheal tubes with an 8-mm inside diameter were wrapped with aluminum adhesive foil tape (No. 425, 3M Corp., St. Paul, Minn.) (No. 1) or with 1-mil copper adhesive foil tape (Venture Tape, Rockland, Mass.) (No. 2) (3). The other tracheal tubes studied were a Mallinckrodt (Argyle, N.Y.) Laser-Flex stainless steel metallic endotracheal tube with a 7-mm inside diameter (No. 3), and a polyvinylchloride (PVC) (Mallinckrodt Hi-Lo, Argyle, N.Y.) endotracheal tube with a 7-mm inside diameter that was covered with a Laser-Guard (Merocel Corp., Mystic, Conn.) protective coating (No. 5). The Laser-Guard consists of a self-adhesive, corrugated silver foil sheet bonded to a thin, absorbent sponge layer, which was saturated with water according to the manufacturer's instructions after its application to the tracheal tube. A ring stand was used to hold the straightened endotracheal tubes vertically. They were centered within identical cardboard cylinders with 45-mm diameter and 115-mm length. The laser was aimed to reflect from the endotracheal tube shaft surface at a 45° angle onto the cardboard (Figure 1). All trials were conducted in

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Address correspondence to Dr. Sosis, Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, 1753 West Congress Parkway, Chicago, IL 60612.

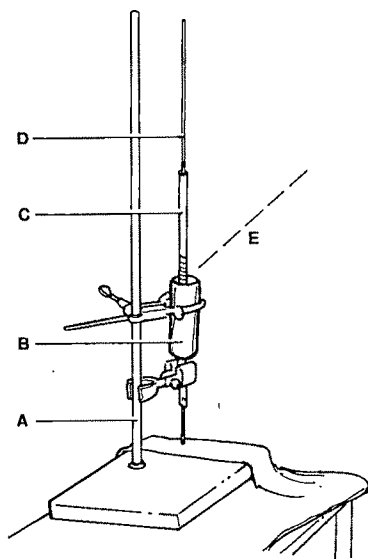


Figure 1. Apparatus for determining the intensity of CO₂ laser reflection from laser-resistant endotracheal tubes. A ring stand (A) supports cardboard cylinders (B) that have been centered around the endotracheal tube (C) under study. A metal rod (D) was used to straighten the endotracheal tube. The laser radiation (E) is directed at a 45° angle onto the endotracheal tube until combustion of the cardboard cylinder occurs because of the reflected laser beam.

Table 1. Times to Combustion of Cardboard Cylinders by CO₂ Laser Reflection

Tracheal tube type	Time (s)
RR + 3M No. 425 Al wrap	1.41 ± 0.54 ^{a,d}
RR + Venture Cu wrap	1.73 ± 0.93 ^{b,c}
PVC + Laser-Guard coating	3.70 ± 2.18 ^{a,b,e}
Mallinckrodt Laser-Flex	9.26 ± 3.40 ^{c,d,e}

RR, red rubber; PVC, polyvinylchloride; Al, aluminum; Cu, copper.

^a*P* < 0.01, RR plus 3M No. 425 and PVC plus Laser-Guard coating.

^b*P* < 0.02, RR plus Venture copper wrap and PVC plus Laser-Guard coating.

^c*P* < 0.05, RR plus Venture copper wrap and Mallinckrodt Laser-Flex.

^d*P* < 0.01, RR plus 3M No. 425 aluminum wrap and Mallinckrodt Laser-Flex.

^e*P* < 0.01, PVC plus Laser Guard coating and Mallinckrodt Laser-Flex.

an atmosphere of room air only. Ten trials on each tube were done. The times to combustion perforating the cardboard were recorded. One-way analysis of variance was used to determine statistically significant differences between mean times. A *P* value less than 0.05 was considered statistically significant.

Results

The results of this study are summarized in Table 1. None of the foil-covered or specially designed tracheal tubes used in this experiment was damaged by

incident CO₂ laser radiation. Reflection of the laser from the aluminum- and copper-foil-wrapped tracheal tubes resulted in combustion of the cardboard cylinder in 1.41 ± 0.54 (mean ± SD) and 1.73 ± 0.93 s, respectively (NS). Reflection from the Laser-Guard silver covering resulted in combustion after 3.70 ± 2.18 s, a significantly longer interval than that of the aluminum foil (*P* < 0.01) or of the copper foil (*P* < 0.02). Laser application to the Mallinckrodt Laser-Flex tracheal tube caused a reflection that resulted in combustion after 9.26 ± 3.40 s, a significantly greater interval than with the Laser-Guard covering (*P* < 0.01), the aluminum foil (*P* < 0.01), or the copper foil (*P* < 0.05).

Discussion

Laser radiation is being used increasingly in medicine because of its power, the precision with which it can be used to ablate lesions, and its intrinsic hemostatic effects. Laser radiation often has the property of being collimated, i.e., the beam does not diverge. The collimation and intensity of the laser have led to the recommendation that blackened instruments be used during this type of surgery to prevent laser reflection. The metallic foil tapes that have been recommended for the protection of combustible tracheal tubes during laser surgery (3) appear reflective, whereas Laser-Guard-protected tracheal tubes and Mallinckrodt stainless steel Laser-Flex tracheal tubes appear less reflective. This study evaluated the reflectivity of these special and protected tracheal tubes.

The combustion of a cardboard cylinder employing a standardized technique of evaluating the reflection of the CO₂ laser from the tracheal tubes was used as a model for evaluating tracheal tube reflection of the CO₂ laser.

The reflectivity of laser radiation from a smooth surface has been considered by Van Der Spek et al. (6). They state that for an incident laser beam of intensity *I_i*, the intensity of the reflected beam (*I_r*) is given by the equation: *I_r* = *I_i* - *I_a*, where the transmission of the beam through the conductor is negligible, and where *I_a* is the amount of beam absorbency in the conductor. Increased absorbency of the beam energy by an irradiated object decreases the energy reflected and will increase the temperature of the absorbing medium.

In our study, the Laser-Guard-wrapped PVC and Laser-Flex tracheal tubes were superior to the 3M No. 425 aluminum- or Venture copper-foil-wrapped PVC tracheal tubes in absorbing the laser beam's energy and increasing the time to combustion by the reflected beam. Silver has a high thermal and electrical

conductivity and the stainless steel shaft of the Laser-Flex tracheal tube is thicker than the aluminum or copper foils; hence, it has a greater thermal capacity. Unintended laser damage to tissues by reflection of the radiation as shown in this experiment is possible when metallic endotracheal tubes or foil surfaces are used to prevent direct laser-induced endotracheal tube combustion.

Our results suggest that the Laser-Guard-wrapped PVC or Mallinckrodt Laser-Flex products are superior to the aluminum or copper foil tapes studied here with regard to the amount of reflected CO₂ laser energy they may allow onto the upper airway. They provide protection from the CO₂ laser-induced airway fires (4,5) and have a low risk of tissue damage from a reflected laser beam.

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Deliberate Hypotension With Nicardipine or Nitroprusside During Total Hip Arthroplasty

Jean-Marc Bernard, MD, Michel Pinaud, MD, PhD, Thierry François, MD, Michel Babin, MD, Isabelle Macquin-Mavier, MD, and Joseph Letenneur, MD

Département d'Anesthésie-Réanimation Chirurgicale and Clinique de Traumatologie et d'Orthopédie, Hôtel-Dieu, Nantes, France; Laboratoire de Pharmacologie Clinique, Hôpital Henri Mondor, Créteil, France

To induce deliberate hypotension during anesthesia, nicardipine was administered to patients undergoing total hip arthroplasty and was randomly compared with nitroprusside. Hemodynamic measurements were performed before and 10, 20, 30, and 60 min after starting to administer either nicardipine ($n = 12$) or nitroprusside ($n = 12$) (B, T1, T2, T3, and T4, respectively); at the end of drug infusion (T5); and 10, 20, and 60 min later (T6, T7, and T8, respectively). Plasma renin activity and catecholamine levels were measured at B, T1, T5, T6, and T7. In addition, plasma nicardipine concentration was measured in five patients at T1, T2, T5, T7, and T8. As with nitroprusside, nicardipine administration ($1-3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, after a titration dose of $4.7 \pm 1.5 \text{ mg}$) resulted in hypotension (up to $-34\% \pm 3\%$), a decrease in systemic vascular resistances (up to $-49\% \pm 4\%$), and increases in heart rate (up to $+17\% \pm 6\%$), cardiac index (up to $+37\% \pm 8\%$), plasma norepinephrine (up to $+63\% \pm 17\%$) and epinephrine (up to $+232\% \pm 68\%$) levels, and plasma renin

activity (up to $+336\% \pm 207\%$). Ten and 20 minutes after discontinuation of the hypotensive drug, nicardipine led to persistent vasodilation and hypotension, which differed significantly from the hypertensive rebound observed after nitroprusside discontinuation, despite a similar increase in plasma renin activity and catecholamine levels. Our results indicate that after the infusion was terminated, the nicardipine-induced vasodilation was opposed to the vasoconstrictive effects of angiotensin II and catecholamines, thus avoiding hypertensive rebound. During infusion, plasma nicardipine concentration was 89 ± 14 (T1), 88 ± 19 (T2), and $205 \pm 52 \text{ ng/mL}$ (T5); and after its discontinuation, 88 ± 10 (T7) and $31 \pm 3 \text{ ng/mL}$ (T8), i.e., effective therapeutic levels. We conclude that nicardipine can be used to induce deliberate hypotension during total hip arthroplasty but results in cumulative effects that persist after the discontinuation of infusion, with a possibility of postoperative hypotension.

(Anesth Analg 1991;73:341-5)

Nicardipine is a water-soluble, photoresistant, dihydropyridine calcium channel blocker that exhibits potent systemic and coronary artery vasodilatory effects (1). Nicardipine administration does not result in negative inotropic, chronotropic, or dromotropic effects (1). Its distribution and elimination half-lives are relatively short after a single intravenous bolus, close to 10 min and 1 h, respectively (2). Although there is extensive worldwide experience with nicardipine for the treatment of hypertension, only limited information is available on its use to induce deliberate hypotension and to atten-

uate bleeding during surgical procedures. Calcium channel blockers, verapamil (3) and diltiazem (4), may produce severe negative chronotropic and dromotropic effects when used to induce deliberate hypotension and therefore remained unusable.

This study was designed to describe the hemodynamic, catecholamine, and renin angiotensin responses to nicardipine-induced hypotension. As nitroprusside is a commonly used drug for deliberate hypotension, these effects were compared with those of nitroprusside in surgical patients during fentanyl-nitrous oxide anesthesia.

Methods

The protocol was approved by our human investigation committee. After consent was obtained, 24 ASA physical status I or II patients (12 men and 12 women) were studied for management of total hip arthroplasty. Patients were randomly assigned to receive

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Address correspondence to Dr. Pinaud, Département d'Anesthésie-Réanimation Chirurgicale, Hôtel-Dieu, 44035 Nantes Cédex 01, France.

either nicardipine ($n = 12$) or nitroprusside ($n = 12$). Patients suffering from hypertension or coronary diseases were not accepted. Patients taking diuretics, calcium channel blockers, or β -adrenergic blockers were excluded from the study.

After oral premedication with diazepam (10 or 15 mg according to a body weight of <70 kg or >70 kg, respectively), anesthesia was intravenously induced with thiopental (5 mg/kg) and fentanyl (5 $\mu\text{g/kg}$), followed by intravenous vecuronium bromide (0.1 mg/kg) to facilitate tracheal intubation. No atropine was given. Lungs were mechanically ventilated with an oxygen/nitrous oxide mixture (inspired oxygen fraction = 0.5). The end-tidal carbon dioxide tension (Normcap, Datex, Finland) was maintained between 32 and 40 mm Hg. Additional fentanyl was given every 10 min in doses of 1.5 $\mu\text{g/kg}$ from anesthetic induction to the end of the operation, except for a dose of 5 $\mu\text{g/kg}$ given at the time of skin incision.

Throughout anesthesia, heart rate (HR) was monitored by a V_5 electrocardiogram lead. A Teflon cannula was inserted into the radial artery for systolic and diastolic arterial blood pressure measurements. A 7.5F triple-lumen thermodilution catheter was inserted through the right jugular vein to measure right atrial pressure, mean pulmonary arterial pressure, and pulmonary capillary wedge pressure (PCWP). The cardiac output was measured by thermodilution using iced injectate in triplicate.

Administration of nicardipine (20 mg in 40 mL of 5% dextrose) or nitroprusside (concentration = 100 mg/L) was started before surgical incision. As supported by Wallin's dose-ranging studies (5,6), a titration dose of nicardipine (10 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was administered until the mean arterial blood pressure (MAP) reached 50–60 mm Hg. The initial infusion rate was then reduced. Nitroprusside was administered at an initial rate of 1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. For each hypotensive drug, the infusion rate was modulated to stabilize MAP at 50–60 mm Hg. The hypotensive drugs were discontinued abruptly just before the prosthesis was cemented in place. Polygeline was infused intravenously to maintain PCWP at greater or equal to 5 mm Hg. Blood replacement (packed red blood cells) was begun when blood loss exceeded 500 mL. Operative blood loss was assessed by weighing sponges, measuring suction drainage, and estimating the amount of blood in the area of the wound. This was determined blindly by nurses unaware of which drug was being used.

Hemodynamic measurements were performed as follows: (a) baseline data, after induction of anesthesia (B); (b) 10, 20, 30, and 60 min after starting to administer nicardipine and nitroprusside (T1, T2, T3, and T4, respectively); (c) just before cementing the prosthesis at the end of the hypotensive drug admin-

istration (T5); and (d) 10, 20, and 60 min after nicardipine and nitroprusside were discontinued (T6, T7, and T8, respectively). The skin incision was performed after T2 in all patients. In addition, at B, T1, T5, T6, and T7, arterial blood samples were drawn for determination of plasma renin activity (PRA) and plasma catecholamine levels. Plasma renin activity was measured by the method of Haber et al. (7) using an angiotensin I radioimmunoassay kit (SB-REN-1 CEA SORIN). Norepinephrine and epinephrine plasma concentrations were measured with a double-isotope enzymatic assay (8) with a sensitivity of 1.5 pg/mL for both epinephrine and norepinephrine. In five patients in the nicardipine group, arterial blood samples were also drawn for determination of plasma nicardipine concentrations at T1, T2, T5, T7, and T8. Plasma nicardipine concentrations were measured by gas-chromatography using an electron capture detector (9). The between-day reproducibility was equal to 11.8% at 5 ng/mL and 6.8% at 75 ng/mL. The response was linear at least between 0 and 200 ng/mL. The limit of quantification was 0.5 ng/mL.

Derived values such as MAP, cardiac index, and systemic vascular resistance index, were computed according to standard formulas (10). Comparisons were made by analysis of variance for repeated measurements when the two factors involved were treatment (nicardipine and nitroprusside) and time. After a significant F-statistic, multiple comparisons within and between groups were performed using Scheffé's method. Unpaired t -tests were used to compare demographic data, the cumulative dose of hypotensive drugs, the duration of their administration, blood loss, and fluid replacement. The level of significance was set at 0.05. Data are presented as mean \pm SEM.

Results

No differences were observed between groups with respect to age, sex, weight, duration of administration, and the cumulative dose of hypotensive agents (Table 1). The loading dose of nicardipine was 4.7 ± 1.5 mg. The average time required to obtain the desired level of hypotension was 7 min (range, 5–9 min). The infusion rates of nicardipine and nitroprusside were, respectively, 1.1 ± 0.2 and 1.3 ± 0.2 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ from T1 to T2; 1.3 ± 0.2 and 2.4 ± 0.7 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ from T2 to T3; 1.4 ± 0.3 and 2.9 ± 0.6 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ from T3 to T4; and 2.8 ± 0.6 and 4.2 ± 0.8 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ from T4 to T5. The cumulative volume of the polygeline and packed red blood cells administered was 1260 ± 126 mL in the nicardipine group and 2110 ± 208 mL in the nitroprusside group ($P < 0.01$). No differences were observed in blood loss during the operation (Table 1).

Table 1. Summary of Procedures

	Nicardipine (n = 12)	Nitroprusside (n = 12)
Age (yr)	68 ± 2	65 ± 3
Weight (kg)	67 ± 3	68 ± 3
Sex ratio	6 M; 6 F	6 M; 6 F
Duration of the administration of the hypotensive agent (min)	89 ± 6	87 ± 6
Cumulative dose of the hypotensive agent (mg)	16.2 ± 2.1	16.8 ± 2.3
Blood loss (mL)	415 ± 70	428 ± 120
Transfusion (n)		
No units	11	10
One unit	1	1
Two units	0	1

All values are mean ± SEM.

The hemodynamic effects are shown in Figure 1. In both groups, hypotension was obtained at T1 and was maintained until the intended end (T5). The lowest individual values of MAP were 50 mm Hg in the nicardipine group and 51 mm Hg in the nitroprusside group. In both groups, hypotension was accompanied by systemic vasodilation, an increase in heart rate, and an increase in cardiac index; there were no significant changes in PCWP, mean pulmonary arterial pressure, and right atrial pressure. Ten and 20 minutes after discontinuation of nicardipine, MAP remained lower than the baseline value and was associated with systemic vasodilation and an increased cardiac index and HR. Ten and 20 minutes after nitroprusside infusion was discontinued, there was a significant increase in MAP above baseline values. Except for MAP at T6 and T7, there were no significant differences between groups. No complications during or after the study were observed in either group.

Hormonal data are shown in Figure 2. In both groups, there was an increase in PRA from T1 to T7 and in plasma epinephrine and norepinephrine levels at T5 and T6. For nicardipine, the plasma norepinephrine concentration remained higher than at baseline at T7. There were no significant differences between groups with respect to the hormonal data.

Plasma nicardipine concentration was 89 ± 14 ng/mL at T1, 83 ± 10 ng/mL at T2, 205 ± 52 ng/mL at T5, 88 ± 19 ng/mL at T7, and 31 ± 3 ng/mL at T8.

Discussion

The hemodynamic and hormonal effects of nitroprusside-induced hypotension were similar to those previously described with this drug, i.e., marked vasodilation, increased cardiac output and HR (4), and an increase in plasma catecholamine levels and in PRA

(11). After abrupt discontinuation of nitroprusside and reduction of anesthetic depth, hypertensive rebound was observed, resulting from persistent increased PRA and catecholamine levels (12,13). Nicardipine administration resulted in hypotension, systemic vasodilation, and increases in HR, cardiac output, plasma catecholamine concentrations, and PRA, similar to those of nitroprusside. During the early stages of both nicardipine- and nitroprusside-induced hypotension, no significant changes in HR were observed, which may be explained by the doses of fentanyl initially administered especially before the operation started. Finally, nicardipine allowed us to reach the desired level of hypotension quickly. After an average titration dose of 5 mg, nicardipine in increasing doses from 1 to $3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ was apparently as potent and as easy to use as nitroprusside in reducing arterial blood pressure. Bleeding was similar in both groups.

However, as the intravenous fluid volume required to maintain PCWP at least equal to 5 mm Hg in both groups was larger in the nitroprusside group than in the nicardipine group, the vasodilatory effects of nicardipine were probably mostly arterial, in contrast to the arterial and venous effects of nitroprusside (14). In addition, nitroprusside immediately resulted in increased cardiac output. With nicardipine, the increase in cardiac output was delayed despite a decrease in afterload. As the filling pressure and HR were unchanged, this finding suggests a slight myocardial depressant effect of nicardipine, which was detectable only during the first 30 min of its administration when surgical stimulation was absent or low and when fentanyl was given at an average dose of $13 \mu\text{g}/\text{kg}$. Like other dihydropyridine calcium channel blockers, nicardipine has negative inotropic properties *in vitro* (15), which are counterbalanced *in vivo* and in conscious subjects by transient compensatory reflex (16). However, if some decrease in myocardial contractility and an absence of effect on venous capacity during nicardipine infusion are the most reasonable explanations for the observed cardiovascular changes, a modified pressure-volume curve and therefore an inadequate preload cannot be excluded.

Our results 10 and 20 min after discontinuation indicate that nicardipine differed significantly from nitroprusside. Under our experimental conditions (i.e., abrupt withdrawal of hypotensive drugs), persistent hypotension and vasodilation after nicardipine and a hypertensive rebound after nitroprusside were observed. No clinical complications owing to the hypotension in the nicardipine group and the hypertension in the nitroprusside group were observed. It is well established that rapid disappearance of nitroprusside leads to unopposed effects of high plasma levels of angiotensin II and catecholamines

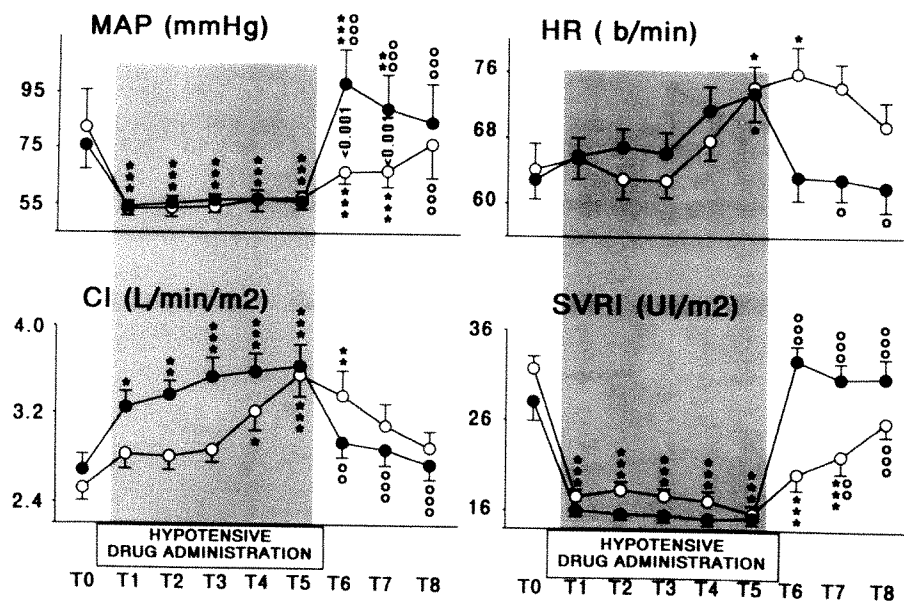


Figure 1. Changes in heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), and systemic vascular resistance index (SVRI) at baseline (T0), during (T1, T2, T3, T4, T5), and after (T6, T7, T8) nicardipine (○) and nitroprusside (●) administration. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, vs baseline. ° $P < 0.05$; °° $P < 0.01$; °°° $P < 0.001$, vs T5.

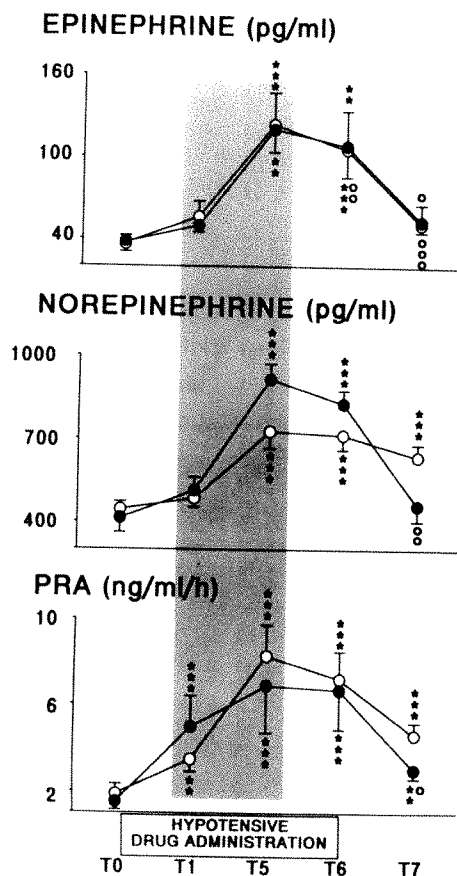


Figure 2. Changes in plasma renin activity (PRA) and in plasma epinephrine and norepinephrine levels at baseline (T0), during (T1, T5) and after (T6, T7) nicardipine (○) and nitroprusside (●) administration. ** $P < 0.01$; *** $P < 0.001$, vs baseline. ° $P < 0.05$; °° $P < 0.01$; °°° $P < 0.001$, vs T5.

(12,13). This results in hypertensive rebound that can be counteracted by small doses of β -adrenoceptor antagonists (13). In our study, the same hemodynamic support, i.e., similar increase in PRA and plasma catecholamines levels, failed to increase arterial blood pressure in the nicardipine group. Therefore, our results indicate that nicardipine can be used to induce deliberate hypotension during the operation but results in less evanescent effects than nitroprusside, leading after the operation to persistent hypotension despite significant increase in PRA and catecholamines. Finally, 1 h after drug discontinuation, there were no significant hemodynamic differences between nicardipine and nitroprusside.

The therapeutic range of nicardipine is reached when the plasma concentration is above 20 ng/mL (17). Although we measured plasma nicardipine in only five patients, our results suggest that, after administration was stopped, significant hypotension, vasodilation, and increased HR were due to persistent plasma nicardipine levels. In addition, the elimination half-life of nicardipine (1 h after a single intravenous bolus) increases significantly when a continuous intravenous infusion is administered, reaching a range of 4–8 h (1). Furthermore, operation and anesthesia may interfere with drug disposition, leading to a decrease in systemic clearance and an increase in plasma concentration (18). Consequently, continuous administration of nicardipine to induce deliberate hypotension during anesthesia may result in cumulative effects that persist after the discontinuation of infusion. Further studies are needed to

establish whether nicardipine can also be used to induce deliberate hypotension during operations of long duration or during other anesthetic paradigms without inducing adverse effects such as too great a decrease in arterial blood pressure or low cardiac output.

This study is the first clinical report showing that a calcium channel blocker, nicardipine, can be used to induce deliberate hypotension. During fentanyl-nitrous oxide anesthesia and operations of relatively short duration, a moderate level of hypotension was easy to obtain and maintain. However, nicardipine may result in cumulative effects, with the possibility of persistent vasodilation and hypotension. Thus, our results suggest that nicardipine is not an ideal agent in controlling arterial blood pressure because of its inability to promptly increase arterial blood pressure by reducing the infusion rate.

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Venous Air Embolism During Lumbar Laminectomy in the Prone Position: Report of Three Cases

Maurice S. Albin, MD, MSc (Anes), Richard R. Ritter, MD, Chester E. Pruett, MD, and Karin Kalff, MD

Department of Anesthesiology, University of Texas Health Science Center, San Antonio, Texas

The possibility that venous air embolism (VAE) may occur during surgical procedures in the prone position is quite remote. This is because virtually no gravitational gradient exists between the incisional area and the right side of the heart and because the relatively high central venous pressure generated in the prone position would further interdict the chance of VAE. We present three patients in whom VAE occurred in the prone position during lumbar laminectomy.

Case Reports

Table 1 compares the salient demographic characteristics of the three patients.

Case 1

After induction of anesthesia, the patient was moved to the operating table and positioned onto a Hasting's frame. The induction and maintenance of anesthesia were uneventful for 5 h; arterial blood pressure (BP) at that time was 135/80 mm Hg; heart rate, 60 beats/min; controlled ventilation with a minute volume of 8 L; central venous pressure, 0; P_{aO_2} , 210 mm Hg; and P_{aCO_2} , 38 mm Hg. The estimated blood loss of 1850 mL was replaced with 3 U of packed red cells and 3 U of fresh frozen plasma. Five hours and 15 min after induction of anesthesia, the precordial Doppler was activated, the BP decreased to 110/60 mm Hg, heart rate remained at 60 beats/min, and 4 mL of air was aspirated from the multi-orificed catheter's central line. Unfortunately, the capnograph malfunctioned making it not possible to obtain a reading at the time of Doppler activation. The area about the epidural veins was flooded; he-

mostasis was checked; the N_2O -isoflurane mixture was discontinued; and 100% O_2 was inspired. No further episodes of VAE occurred during the remaining 4 h of the operation, and the patient recovered uneventfully.

Case 2

After induction of anesthesia, the patient was turned prone and placed on a four-poster frame. Induction and maintenance of anesthesia were problem-free for 5 h and 25 min, at which time vital signs showed a BP of 100/60 mm Hg, normal sinus rhythm, heart rate of 96 beats/min, controlled ventilation with a minute volume of 7.5 L, and an estimated blood loss of 800 mL. Five minutes later, bradycardia and hypotension progressed to asystole. The patient was then turned supine and cardiopulmonary resuscitation was instituted to no avail with death ensuing. An autopsy performed 24 h later indicated the presence of air bubbles in the coronary blood vessels. When the pericardium was opened under water and the right ventricle was excised, 40 mL of air exited. The autopsy noted massive air embolism as the cause of death. The postmortem report did not indicate whether a probe patent foramen ovale was present or whether air was present in the great vessels or other heart chambers.

Case 3

The patient was placed prone on a four-poster frame after induction of anesthesia and was stable for approximately 3 h and 50 min after surgical incision, with a BP of 130/75 mm Hg, heart rate of 60 beats/min, and ventilation controlled with a minute volume of 7 L. The O_2 saturation was 98%; central venous pressure, 8.0 mm Hg; end-tidal CO_2 ($EtCO_2$), 36.0 mm Hg; estimated blood loss, 2.5–3 L; and the patient received 3.9 L of lactated Ringer's solution and 1.25 L of blood through a Cell Saver. Five minutes later, a sudden "whirring" noise was heard

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Address correspondence to Dr. Albin, Department of Anesthesiology, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284.

Table 1. Demographic Variables

	Patient 1	Patient 2	Patient 3
Age (yr)	55	40	40
Weight (kg)	113	137	105
Sex, ASA	M,II	M,II	M,II
Past history	Hypertension, DM, mild COPD, lumbar laminectomy once	Hypertension, lumbar laminectomy once	Former smoker, lumbar laminectomy twice
Proposed surgery	Lumbar laminectomy with fusion L4-5	Lumbar laminectomy with fusion L3-4	Lumbar laminectomy with fusion L5-S1
Monitoring	ECG, BP cuff (automatic), esophageal stethoscope, temperature probe, capnograph, arterial line, central line, precordial Doppler	ECG, BP cuff (automatic), esophageal stethoscope, mass spectrometer (old, no continuous CO ₂), temperature probe	ECG, BP cuff (automatic), pulse oximeter, esophageal stethoscope, capnograph, central line (double lumen)
Central line	Multiorificed, localized by x-ray with tip at junction of right atrium-superior vena cava	None	Single orifice, double lumen, tip in proximal right atrium
Anesthesia	Thiopental, fentanyl, diazepam, 50% N ₂ O, halothane, isoflurane, pancuronium	Thiopental, fentanyl, 70% N ₂ O, isoflurane, atracurium	Midazolam, thiamylal, sufentanil, 50% N ₂ O, atracurium
Position	Hasting's (Canadian) frame	Four-poster frame	Four-poster frame
Outcome	Survived	Died	Died
Postmortem findings		Air in coronary arteries, 40 mL air in right ventricle	Massive air in coronary arteries, heart, spinal cord, cerebral and mesenteric circulation; <i>probe-closed</i> foramen ovale

M, male; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; BP, blood pressure; RA, right atrium; SVC, superior vena cava; ASA, American Society of Anesthesiologists risk classification.

through the esophageal stethoscope. The electrocardiogram exhibited a left ventricular strain pattern and ST depression. Aspiration of the central line was negative, the N₂O and isoflurane were discontinued, and 100% O₂ was instituted. The EtCO₂ decreased precipitously to less than 10 mm Hg in 1 min and then to 0 mm Hg. The systolic BP decreased to 60 mm Hg and then was unrecordable. The patient was turned supine, and cardiopulmonary resuscitation was carried out for 45 min but was ineffective and the patient died. The pathological diagnosis derived from an autopsy indicated that massive air embolism was the cause of death. Air bubbles were seen throughout the vasculature of the cerebral circulation, the coronary arteries, the arborization of the mesenteric vessels, and along the course of the anterior spinal artery. The right ventricle was virtually collapsed, and when opened under water, a few large bubbles of air were noted. The foramen ovale was examined and found to be *probe-closed*.

Discussion

Venous air embolism in the prone position (with a fatal outcome) was first reported in 1969 by Shenkin

and Goldfedder (1) during a craniotomy for a posterior fossa exploration in which the head was elevated 10 cm above the heart level and 10 cm H₂O of negative pressure was applied to the expiratory phase using a Bird ventilator. Meridy et al. (2) reviewed the complication seen during neurosurgery in the prone position, evaluating 120 procedures in 107 children. Although neither a precordial Doppler nor central line was available, the diagnosis of VAE was made on clinical grounds in two patients. Albin et al. (3) described the occurrence of VAE in a patient undergoing laminectomy in the prone position with a gravitational gradient not exceeding 5 cm.

One of the critical factors in all three patients relates to the type of positioning used to secure the prone position. The use of the Hasting's (Canadian) (4) frame and the four-poster frame (5) both decrease the intraabdominal pressure and increase the interlaminar space in the lumbar spine (6). In both positions, the abdomen hangs free and the lower extremities are dependent. Furthermore, the legs need to be wrapped to avoid pooling of blood. DiStefano et al. (7) evaluated the vena caval pressures in six variants of the prone position used for low back surgery and found that patients in the Hasting's frame generated

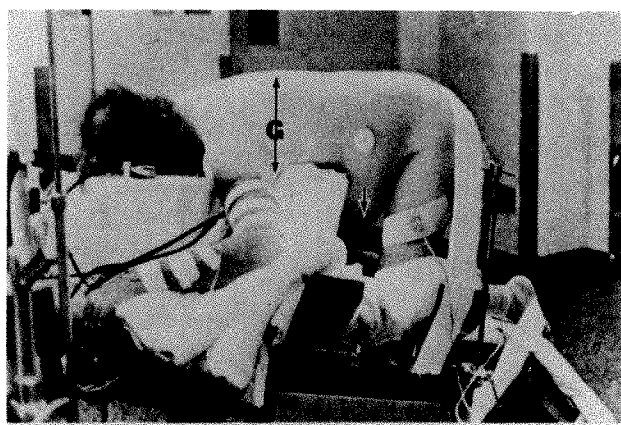


Figure 1. Patient in prone position using the Hasting's (Canadian) frame. Note the unimpeded abdomen (arrow) and the gravitational gradient (G) that exists between the area of the spinous process and the right side of the heart. (Reprinted with permission of publisher. Copyright 1978, American Medical Association. From Albin MS et al. Atrial catheter and lumbar disk surgery. JAMA 1978;239:496.)

caval pressures ranging from +2.0 to -6.6 cm H₂O. One may speculate that similar caval pressures would be obtained in the four-poster position as there is also no restriction on movement of the abdomen. One must also realize that a considerable gravitational gradient can exist between the right side of the heart and the vertebra in the prone position (Figure 1). In patient 1, the gradient was calculated to be 15 cm. In the face of an increased gravitational gradient, a contracted blood volume, or inadequate intravascular volume replacement and a position that would enhance a negative caval pressure, the ingredients necessary to favor the entrainment of air into the venous circulation are present.

The entrance of air was indeed a sudden occurrence in all three patients. In patient 1, air was detected early by use of the Doppler; in patient 2, there was no premonitory warning; and in patient 3, a "whirring" sound was perceived through the esophageal stethoscope just before cardiac arrest. The "whirring" sounds correspond to the classical "churning" (millwheel) murmur described by Erichsen in 1844 (8). In animal experiments using air infusion, Adornato et al. (9) described the exquisite sensitivity of the ultrasonic Doppler for air bubble detection at an infusion rate of 0.02 mL·kg⁻¹·min⁻¹. In contrast, the esophageal stethoscope can detect the "millwheel" murmur at the rate of 1.7 mL·kg⁻¹·min⁻¹ being 35 times less sensitive (9). Albin and coworkers (3) have indicated that the precordial Doppler can detect less than a 0.1-mL volume of air passing its beam in a 70-kg individual for a sensitivity of 0.0014 mL/kg. End-tidal CO₂ quickly decreased in patient 3; Chang et al. (10) and

Gildenberg et al. (11) found that EtCO₂ ranks second to the precordial Doppler in terms of sensitivity of routine monitoring for air bubble detection (12). The EtCO₂ was not available in patient 1 because of a malfunctioning capnograph. In patient 2, it was part of an old mass spectroscopy system that did not give a continuous EtCO₂ output. Although the postmortem findings in patient 2 indicated VAE as the cause of death, the autopsy unfortunately was not complete in that the pathologist neglected to evaluate the probe-patency of the foramen ovale. Hagen et al. (13) studied 965 autopsy specimens of human hearts and described the overall incidence rate of patent foramen ovale to be 27.3% with a mean potential diameter of 4.9 mm. The nonexistence of a probe-patent foramen ovale in patient 3 indicated the transpulmonary movement of VAE into the left side of the heart. Marquez et al. (14) described a death due to VAE occurring in the sitting position during posterior fossa surgery in which the autopsy showed a non-probe-patent foramen ovale.

Butler and Hills (15,16) have done pioneering work in delineating the conditions under which the transpulmonary passage of venous air emboli occurs. They demonstrated a threshold in dogs in which air infusion rates below 0.3 mL·kg⁻¹·min⁻¹ allowed complete filtration of the bubbles by the lung. However, at air infusion rates above 0.3 mL·kg⁻¹·min⁻¹, spillover into the arterial circulation occurred in 50% of the animals. When air infusion was increased to 0.4 mL·kg⁻¹·min⁻¹, 70% of the animals demonstrated that the transpulmonary passage of air emboli occurred (16). Butler and Hills also noted that pulmonary vasodilators (aminophylline) enhanced transpulmonary passage (15). That the bubble breakthrough phenomenon may involve a degree of species specificity can be seen in the study of Vik and coworkers (17) who used a pig model because of the similarity of the porcine vasculature and physiologic responses to those of humans. They found that the threshold for bubble breakthrough in the pig occurred at an infusion rate of 0.1 mL·kg⁻¹·min⁻¹, on an order of magnitude three times less than that found by Butler and Hills (16). The mean transit time (from beginning of an infusion to start of bubble breakthrough) was 15.4 ± 1.9 (SE) min in one group and 17.2 ± 9.2 (SE) min in another group of animals. In one infusion group (0.1 mL·kg⁻¹·min⁻¹), the total air volume infused to produce bubble breakthrough was 36 mL; and in a second infusion group (0.2 mL·kg⁻¹·min⁻¹), it was 81.6 mL. In both studies of Butler and Hills (16) and Vik et al. (17), there were marked increases in pulmonary artery pressures and pulmonary vascular resistances whereas mean arterial blood pressures and cardiac outputs decreased.

The studies of Butler and Hills (15,16) and Vik et

al. (17) indicate that significant volumes of air need to be entrained before transpulmonary passage of air occurs, and their investigations used Doppler technology for air bubble detection. The precordial Doppler has an extraordinary sensitivity and appears to be in the same range as two-dimensional echocardiography (12). Although the Hasting's frame, four-poster frame, or other devices used to free the abdomen from compression in the prone position help to decrease engorgement of the venous plexuses and hence decrease bleeding, the resulting decreased caval pressure can increase the gravitational gradient and hence place the patient at risk for VAE. A depleted blood volume and/or inadequate volume replacement may further enhance the chance for VAE. In the first patient the ability of the precordial Doppler to detect air and the ability to aspirate air using a multiorificed catheter were indicated. Patient 2 demonstrates the rapidity with which air can be entrained and cardiac arrest can develop with little or no premonitory clinical signs. In patient 3, hemodynamic collapse occurred within 1 min after the whirling-millwheel murmur sounds were heard, and no air could be aspirated from either orifice of the double-lumen central line. Unfortunately, the distal lumen orifice of the line was in the proximal right atrium, a location where effective aspiration has been shown to be minimal (18).

These three cases indicate the need for serious consideration of complete monitoring for VAE whenever a patient is placed prone using any of the positioning techniques that allows for free movement of the abdomen. The monitoring methods would include the use of a precordial Doppler, end-tidal CO₂ measurements, and the use of a multiorificed central line in which the tip is localized either at the right atrium-superior vena cava junction or at 2 cm in the right atrium. The central line serves for aspiration and can also be used for central venous pressure monitoring. The efficacy and superiority of the multiorificed catheter for air aspiration have been noted by Colley and Artru (19) as well as by Bunegin et al. (18). It is the practice of the two of us (M.S.A., R.R.R.), to monitor the arterial blood pressure using an indwelling arterial line in all these cases. This allows for a continuous display of arterial blood pressure and for a blood port from which samples can be drawn for analysis of arterial blood gases and other determinations. In patient 2, the concentration of N₂O used was 70%, whereas 50% N₂O was used in the other two patients. It is important to remember that at a 50% N₂O concentration the volume of entrained air is doubled, and at a 70% N₂O concentration the air volume is more than tripled (20). In the past 18 mo, we (M.S.A., R.R.R.) have eliminated N₂O as part of our anesthetic technique in these

cases. We believe that early Doppler-EtCO₂ monitoring and rapid aspiration of a correctly placed central line together with the immediate alerting of the surgeon would help to decrease further entrance and to attenuate the serious sequelae of VAE. Finally, it is important to report these types of cases in the medical literature so that we may be able to perceive an estimate of the *true* incidence rate of VAE under these conditions.

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Lung Laceration After Tracheal Extubation Over a Plastic Tube Changer

Luiz G. R. deLima, MD, and Michael J. Bishop, MD

Departments of Anesthesiology and Medicine (Division of Pulmonary and Critical Care), Harborview Medical Center, University of Washington, Seattle, Washington

Stiff plastic, gum bougie, or woven stylets have become popular as introducers in difficult tracheal intubations and for replacement of endotracheal tubes (1). Additionally, they may be left in the trachea during tracheal extubation of patients with abnormal airway anatomy to assist if emergent reintubation is required. The recommended technique for ascertaining tracheobronchial placement of the bougie is the detection of a firm resistance to further passage of the stylet (2,3).

We report a case of pneumothorax and lung abscess after extubation of the trachea over a plastic tracheal tube changer (TTC) (JEM 400, TTC; Instrumentation Industries, Bethel Park, Penn.) in which the TTC was advanced until a firm resistance was felt.

Case Report

A 38-yr-old man with osteogenesis imperfecta presented for ventriculoperitoneal shunt placement before removal of the odontoid process to relieve brainstem compression. Because of abnormal airway anatomy, sedation and local anesthesia were used to facilitate tracheal intubation over a fiberoptic bronchoscope. The intraoperative course was uneventful. His trachea was extubated in the recovery room but required reintubation because of upper airway obstruction. The reintubation was very difficult.

The following day, the patient was alert, cooperative, and all criteria for tracheal extubation were met. With the cuff deflated, there was a large leak around the endotracheal tube (ETT), and the patient could breathe around the tube when the lumen was occluded.

After instillation of 4% lidocaine down the ETT, a TTC was gently inserted down the ETT until slight resistance was met. The ETT was removed over the

TTC. Gas flow through the TTC was evident and breath sounds were clear and equal bilaterally. Oxygen was supplied via a face mask.

For the first 10 min the patient was comfortable, able to communicate effectively, and had a clear airway and no dyspnea. Soon thereafter he developed respiratory difficulty, with prolonged and forceful expirations. Agitation and tachycardia were noted but there was no apparent upper airway obstruction. Attempts to thread ETTs over the TTC were unsuccessful, the TTC having softened after having been exposed to body temperature for several minutes. As the patient's level of consciousness started to deteriorate, complete airway obstruction developed. Performing laryngoscopy with a Macintosh No. 3 blade opened the airway, but no recognizable structures could be visualized. The heart rate decreased to 52 beats/min and the hollow TTC was connected to oxygen at a flow of 5 L/min, and 1 mg of atropine was given intravenously. Laryngoscopy was unsuccessfully attempted with different blades. Subcutaneous emphysema began to develop. The patient continued to deteriorate and began seizing. Ventilation via a bag and mask and an oral airway was ineffective. Systolic arterial blood pressure decreased to 70 mm Hg with a fraction of inspired oxygen of 1.0. Partial arterial pressure of oxygen was 40 mm Hg, $pH_a = 7.26$, and partial arterial pressure of carbon dioxide was 24 mm Hg. A cricothyrotomy was performed and a 5-mm cuffed ETT was inserted. Breath sounds were not heard over the left side of the chest and chest roentgenogram confirmed a left pneumothorax, which was drained by thoracostomy tube placement. Arterial saturation and arterial blood pressure improved immediately, and the patient recovered consciousness a few hours later.

The patient was taken to the operating room to revise the cricothyrotomy and change it to a tracheostomy. A roentgenogram taken in the recovery room after conversion of the cricothyrotomy to a tracheostomy showed a 2×4 -cm lucency in the midportion of the left lung with the characteristic oval

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Address correspondence to Dr. Bishop, Department of Anesthesiology, Harborview Medical Center, 325 Ninth Avenue, ZA-14, Seattle, WA 98104.

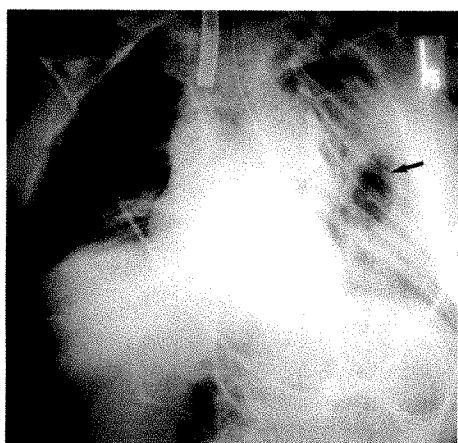


Figure 1. Chest roentgenogram taken after reexpansion of the pneumothorax. Note the persistent ovoid lucency in the left mid-lung field (arrow), characteristic of a lung laceration.

shape of a lung laceration (Figure 1). A moderate amount of air was present in the soft tissues of the chest, but there was no evidence of air in the neck or mediastinum. Subsequently, an abscess developed in the superior segment of the left lower lobe where the 2×4 -cm air lucency had been present. The abscess resolved with antibiotic therapy.

Discussion

This patient had no prior history of lung disease yet a tension pneumothorax developed after placement of the TTC and removal of the ETT. Localized air collection in the central area of the left lung also developed, consistent with lung laceration. Pneumothorax, pneumomediastinum, hydrothorax, bronchopleural fistula, subcutaneous emphysema, and lung abscess have been ascribed to stylets, small-bore feeding tubes, polyvinyl feeding tubes, and other relatively stiff objects introduced into the airway (4,5). Roubenoff and Rovick (6) presented four cases of pneumothorax caused by intrapulmonary placement of small-bore nasogastric feeding tubes, and their review of the literature revealed 106 cases of similar complications. The senior author (M.B.) has seen two

other cases of pneumothoraces after tracheal tube changes over woven stylets (Eschmann gum-elastic bougie). However, in these two cases, underlying lung disease and mechanical ventilation raised questions about a causal relationship. Given the numerous reports of lung trauma with insertion of plastic gastric tubes, it is not surprising that occasional trauma will occur with blunt tracheal tube changers.

Kidd et al. (2) found that firm resistance to passage of a gum elastic bougie was felt between 24 and 40 cm during 100 attempted tracheal intubations. They assumed that the resistance occurred when the bougie reached the small bronchi. We disagree with the recommendation that the bougie or TTC be inserted until there is a firm resistance and suggest that measurement and use of markings to limit the depth of insertion are warranted. A distance of 40 cm from the lips seems potentially hazardous, as a study of 59 subjects found that incisor-carina distances ranged from 23.0 to 31.5 cm (7). Thus, 40 cm could easily result in very peripheral placement of such a stylet. In changing a tube, a distance of no more than 23 cm from the lips should result in good intratracheal position in most patients (8).

In our patient, grossly abnormal anatomy created a very short distance from the lips to the carina and undoubtedly contributed to overly deep insertion of the TTC with consequent laceration of the lung.

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Hematoma After Epidural Anesthesia: Relationship of Skin and Spinal Angiomas

Douglas W. Eastwood, MD

Department of Anesthesiology, Case Western Reserve University, University Hospitals of Cleveland, Cleveland, Ohio

A cervicothoracic epidural hematoma developed immediately after a carotid endarterectomy under cervical epidural anesthesia in an elderly man who was found to have a venous angioma in the epidural space and a cutaneous venous angioma over the left clavicular area. Congenital spinal arteriovenous abnormalities frequently have vascular channels communicating with metamerically cutaneous vascular abnormalities (1-8). A cutaneous angioma may indicate the presence of a hazardous lesion in the epidural or spinal area.

Case Report

A 71-yr-old man was admitted with a history of increasingly frequent transient cerebral ischemia attacks, previous myocardial infarction, irregular rhythm and angina, remote upper gastrointestinal bleeding, and hypertension. Medications included digitalis, quinidine, propranolol, nitroglycerin, and isoptocarpine. Positive findings on physical examination included an arterial blood pressure of 210/110 mm Hg, bruits over both carotid arteries, and a prominent plexus of dilated intracutaneous and subcutaneous veins over the upper left chest and neck reported as present for many years. Emergency carotid angiography was performed, which showed severe stenosis of the left common carotid at the bifurcation and an ulcerated plaque of the right internal carotid above the bifurcation. Treatment was begun with enteric-coated aspirin tablets, 600 mg every 4 h. Laboratory studies were within normal limits including a prothrombin time of 11.7/12.3 s (patient/control) a partial thromboplastin time of 38/35 s, and platelets of $185,000 \text{ mm}^{-3}$. The electrocardiogram showed sinus rhythm, a heart rate of 65 beats/min, poor R-wave progression, and nonspecific ST-T wave changes (digitalis effect) with no changes

from 6 yr previously. Chest radiogram showed chronic diffuse fibrosis.

A left carotid endarterectomy was performed under cervical epidural and skin infiltration anesthesia. The initial placement of an epidural catheter through a No. 17 Tuohy needle using 10 mL of 0.5% bupivacaine resulted in right-sided shoulder and neck anesthesia. Replacement using 3% chloroprocaine in 10-mL increments to a total of 60 mL for the 180-min operation provided satisfactory anesthesia from C2 to T2 bilaterally. No paresthesia or return of blood or cerebrospinal fluid occurred. The surgeon infiltrated the skin with 1% lidocaine. The arterial blood pressure varied between 220/100 and 150/100 mm Hg. Heparin (5000 U) was given intravenously before cross-clamping the carotid artery and the surgery was completed with minimal blood loss. Diazepam (10 mg), fentanyl (200 μg), and 5% dextrose in lactated Ringer's solution (1300 mL) were given intravenously during the 150-min procedure, and the patient remained responsive and comfortable. The epidural catheter was removed intact and the patient was transferred to the recovery room.

The patient, receiving nasal oxygen for 30 min with no changes in vital signs, began to complain of discomfort in the chest, left arm, and upper back. He became restless, diaphoretic, and coughed vigorously producing some frothy pink-tipped sputum. Because of the hypertension, history of myocardial infarction, and fluid volume given during surgery, a diagnosis of left ventricular failure was considered. A portable chest radiogram showed diffuse haziness, which was not significantly changed from the preoperative film. Sublingual nitroglycerin and intravenous fentanyl provided partial relief. Arterial blood pressure remained 200/100 mm Hg and the electrocardiogram was unchanged. Within minutes, left leg weakness developed and progressed to complete motor paralysis. Touch and pain sensation remained on the left leg but were lost on the right leg. The diagnosis of Brown-Sequard syndrome from epidural hematoma was made, and emergency cervical laminectomy was scheduled. The paraplegia became bilateral and arm

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Address correspondence to Dr. Eastwood, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

weakness developed. The systolic blood pressure decreased to 80 mm Hg, requiring fluid, ephedrine, and neosynephrine infusion to restore an arterial blood pressure of 180/80 mm Hg.

About 140 min after completion of the carotid endarterectomy, endotracheal intubation was performed under topical anesthesia. Intravenous fentanyl, ketamine, and pancuronium and inhalation of 50% nitrous oxide and oxygen provided anesthesia. The patient was placed on his left side for the cervical laminectomy. Blood coagulation studies done at this time were unchanged from those done preoperatively. A hematology consultant indicated that no abnormal coagulopathy was present. Large variations in arterial blood pressure required continuous intravenous neosynephrine, intermittent ephedrine, and rapid blood and fluid infusion. An epidural hematoma was found extending from C7 to T3. An extensive plexus of "wormlike" veins covered the dura from C5 to T1. Partial excision and coagulation of the plexus resulted in a 2200-mL estimated blood loss, which was replaced by 1000 mL of blood, 500 mL of platelet concentrates, 1500 mL of 5% dextrose in lactated Ringer's solution, and 500 mL of 5% dextrose in water. With decompression of the spinal cord, the arterial blood pressure stabilized without further vasopressor support.

Postoperatively the patient awakened promptly, was oriented, and had no motor or sensory deficit. He continued to experience occasional angina. Severe chest pain with electrocardiographic changes developed on the third postoperative day and a myocardial infarction was diagnosed. His cardiac status continued to deteriorate until his death 2 wk after surgery. Permission for postmortem examination was not obtained.

Discussion

Although chest, arm, and back pain in the recovery room were first thought to be of cardiac origin, they more likely resulted from spinal cord and nerve root compression from the epidural bleeding. Trauma to the epidural angioma during the placement of the epidural catheter initiated the bleeding. Aspirin for 2 days before surgery and low-dose heparin during surgery are unlikely major contributors to the hematoma as no bleeding from the edges of the wound, hematologic abnormalities, or delayed clotting were identified. Ligation during carotid surgery of venous drainage from the angioma and severe coughing after surgery may have contributed to the extent of the epidural bleeding.

This 1977 event was not reported until now because the relationship of cutaneous and spinal angiomas was not recognized until a chance finding of an

illustration by Netter (8) stimulated the literature search. Twenty percent of patients with congenital cutaneous arteriovenous abnormalities have associated spinal angiomas in the same metamere (4). The metameric relationship is supported in this patient by the common arterial and venous supply to the upper chest wall and the spinal column (5). Vascular abnormalities in relation to the vertebrae, the epidural space, and the spinal cord, although rarely the cause of symptoms, have been reported in 11% of autopsies where the spine has been examined (6) and represent 3%–4% of all symptomatic spinal lesions (7). Spontaneous epidural or subarachnoid hematomas can occur in patients with a spinal angioma after straining or coughing (2). Spinal cord pressure symptoms from enlargement of an angioma are found during the third trimester of pregnancy (9,10). This has been attributed to progesterone and the increased venous pressure exerted by the enlarging uterus (9). Engorgement of the epidural veins also results from obstruction of outflow by a spinal tumor (11).

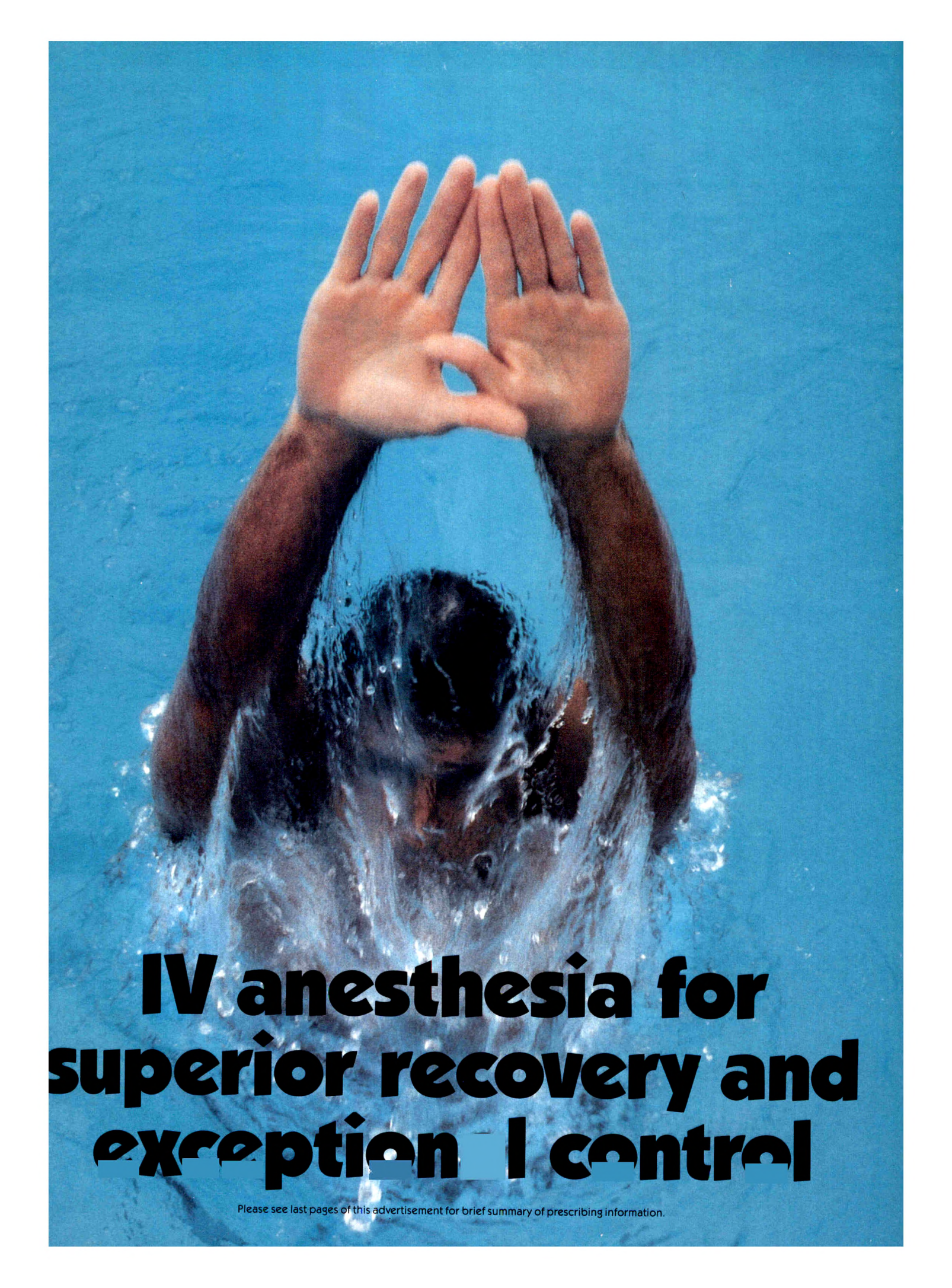
In summary, a hematoma resulted from rupture of an unrecognized epidural venous angioma during epidural anesthesia for a carotid endarterectomy in a patient with a cutaneous angioma in the same metamere. Although aspirin and heparin were administered, abnormal coagulopathy could not be demonstrated. The ligation of venous drainage from the area during the surgery and severe coughing in the postoperative period are probable contributing factors. As vascular abnormalities in the epidural or subarachnoid space are associated with cutaneous angiomas, this relationship should be considered when administering spinal or epidural anesthesia in the same metamere as a cutaneous lesion.

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A photograph of a person swimming underwater, viewed from below. The person's head is submerged, and their arms are raised with hands open and palms facing each other, forming a frame around their face. The water is a clear, vibrant blue, and there are some bubbles and ripples around the person's head and arms.

IV anesthesia for superior recovery and exceptional control

Please see last pages of this advertisement for brief summary of prescribing information.

Superior exceptional

Significantly improved speed and quality of recovery compared with thiopental/isoflurane

Mean postanesthesia recovery times (min) ¹		
	DIPRIVAN	Thiopental/ isoflurane
Duration of anesthesia	85*	57
Response to commands	3.5*	6.1
Fully oriented	5.5	9.4
Able to tolerate fluids	61*	130
"Ready" for discharge	138*	206

—adapted from Korttila et al, p A564¹

*Statistically significant ($P < .05$).

Measurements taken from time of discontinuation of all maintenance anesthesia.

- Majority of patients are generally awake, responsive, and oriented within 8 minutes

recovery and anesthetic control

**Significantly less nausea and vomiting
than with thiopental/isoflurane**

	DIPRIVAN	Thiopental/ isoflurane
Wetchler ²	(n = 20)	(n = 20)
Nausea/vomiting	20%	65%
Sung et al ³	(n = 49)	(n = 50)
Nausea/vomiting	8.1%	30%

As part of a balanced anesthetic technique,
**DIPRIVAN is a cost-effective alternative
to thiopental/isoflurane for induction and
maintenance.**

Please see last pages of this advertisement for brief summary of prescribing information.

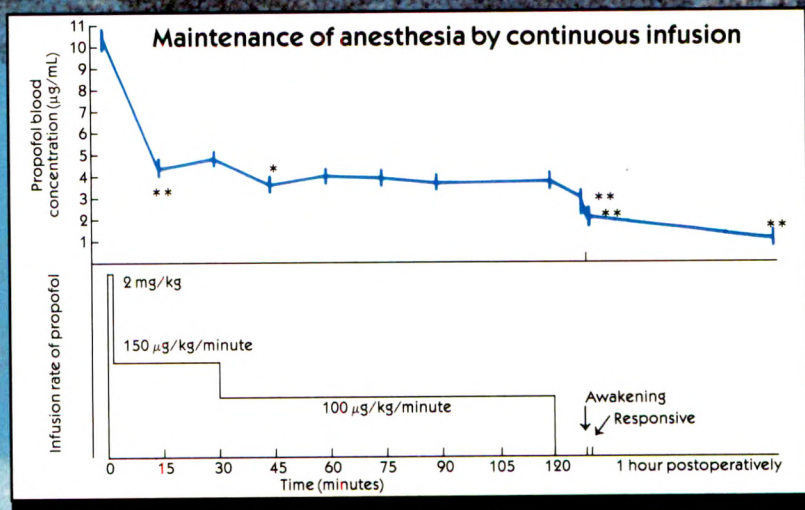
For induction and maintenance

DIPRIVAN[®]
INJECTION *propofol*

Superior exceptional

Maintenance of anesthesia as easily controlled as with isoflurane

- Steady state blood concentrations are proportional to rate of administration



—adapted from Herregods et al, p 364⁴

*Significant difference ($P < .05$) from previous value.

** $P < .02$. (Mean and SEM values are shown.)

After a loading dose of 2 mg/kg, anesthesia was maintained with 150 µg/kg/min for 30 minutes—then 100 µg/kg/min for 90 minutes.⁴

- Total body clearance exceeds estimates of hepatic blood flow⁵
- No active metabolites produced

As with most anesthetic agents, clearance rate of DIPRIVAN decreases in elderly patients.

recovery and anesthetic control

Hemodynamic effects are controllable and dose-dependent

- Blood pressure (BP) predictably decreases on induction (sometimes > 30%) but is within acceptable ranges for healthy individuals*
- Hemodynamic effects during induction are generally more pronounced than with traditional IV induction agents

After initial decreases in BP following induction, hemodynamics return toward baseline

The cardiovascular effects of DIPRIVAN may be increased in patients who have received sedative or narcotic premedications.¹

DIPRIVAN is not a narcotic agent

When used with N₂O/O₂ for maintenance, supplementation with IV analgesic agents is generally required; muscle relaxants may also be required.

Strict aseptic techniques must always be maintained while handling DIPRIVAN. DIPRIVAN is a single-use parenteral product and contains no antimicrobial preservatives. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules are opened. Administration should commence promptly and be completed within 6 hours after the ampules have been opened.

*Elderly, debilitated, and/or hypovolemic patients, and those rated ASA III/IV, may have more profound adverse cardiovascular responses.

¹Induction dose requirements may be reduced.

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For induction and maintenance

DIPRIVAN[®]
INJECTION *propofol*

For induction and maintenance
DIPRIVAN[®]
INJECTION *propofol*

Superior recovery and exceptional anesthetic control

As part of a balanced anesthetic technique,
**DIPRIVAN is a cost-effective alternative to
thiopental/isoflurane for induction and
maintenance.**

- Significantly improved speed and quality of recovery compared with thiopental/isoflurane
- Significantly less nausea and vomiting than with thiopental/isoflurane
- As convenient and as easily controlled as isoflurane for maintenance of anesthesia

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STUART PHARMACEUTICALS
A business unit of ICI Americas Inc.
Wilmington, Delaware 19897 USA

DIPRIVAN[®]

INJECTION

10 mg/mL

propofol

EMULSION FOR IV ADMINISTRATION

(For full prescribing information, see package insert.)

INDICATIONS AND USAGE: DIPRIVAN Injection is an IV anesthetic agent that can be used for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery. DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. (See **PRECAUTIONS**.) DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. (See **PRECAUTIONS**.) DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. (See **PRECAUTIONS**.) DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. (See **PRECAUTIONS**.) **CONTRAINDICATIONS:** When general anesthesia is contraindicated or in patients with a known hypersensitivity to DIPRIVAN Injection or its components. **WARNINGS:** DIPRIVAN Injection should be administered only by persons trained in the administration of general anesthesia. **Facilities for maintenance of a patent airway, artificial ventilation, and oxygen enrichment and circulatory resuscitation must be immediately available.** DIPRIVAN Injection should not be coadministered through the same IV catheter with blood or plasma because compatibility has not been established. In vitro tests have shown that aggregates of the globular component of the emulsion vehicle have occurred with blood/plasma/serum from humans and animals. The clinical significance is not known. **Strict aseptic techniques must always be maintained while handling DIPRIVAN Injection. The vehicle in DIPRIVAN Injection is capable of supporting rapid growth of microorganisms. (See **DOSAGE AND ADMINISTRATION, Handling Procedures.**)** **PRECAUTIONS:** **General:** A lower induction dose and a slower maintenance rate of administration should be used in elderly, debilitated and/or patients with circulatory disorders, and those rated ASA III or IV. (See **DOSAGE AND ADMINISTRATION**.) Patients should be continuously monitored for early signs of significant hypotension and/or bradycardia. Treatment may include increasing the rate of intravenous fluid, elevation of lower extremities, use of pressor agents, or administration of atropine. Apnea often occurs during induction and may persist for more than 60 seconds. Ventilatory support may be required. Because DIPRIVAN Injection is an emulsion, caution should be exercised in patients with disorders of lipid metabolism such as primary hyperlipoproteinemia, diabetic hyperlipemia, and pancreatitis. Since DIPRIVAN Injection is never used alone, an adequate period of evaluation of the awakened patient is indicated to ensure satisfactory recovery from general anesthesia prior to discharge of the patient from the recovery room or to home. When DIPRIVAN Injection is administered to an epileptic patient, there may be a risk of convulsion during the recovery phase. Transient local pain may occur during intravenous injection, which may be reduced by prior injection of IV lidocaine (1.0 mL of a 1% solution). Venous sequelae (phlebitis or thrombosis) have been reported rarely (< 1%). In two well-controlled clinical studies using dedicated intravenous catheters, no instances of venous sequelae were reported up to 14 days following induction. Pain can be minimized if the larger veins of the forearm or antecubital fossa are used. Accidental clinical extravasation and intentional injection into subcutaneous or perivascular tissues of animals caused minimal tissue reaction. Intra-arterial injection in animals did not induce local tissue effects. One accidental intra-arterial injection has been reported in a patient, and other than pain, there were no major sequelae. Perioperative myoclonia, rarely including convulsions and opisthotonus, has occurred in a temporal relationship in cases in which DIPRIVAN Injection has been administered. Clinical features of anaphylaxis, which may include bronchospasm, erythema and hypotension, occur rarely following DIPRIVAN Injection administration, although use of other drugs in most instances makes the relationship to DIPRIVAN Injection unclear. DIPRIVAN Injection has no vagolytic activity and has been associated with reports of bradycardia, occasionally profound. The intravenous administration of anticholinergic agents (eg, atropine or glycopyrrolate) should be considered to modify potential increases in vagal tone due to concomitant agents (eg, succinylcholine) or surgical stimuli. **Information for Patients:** Patients should be advised that performance of activities requiring mental alertness, such as operating a motor vehicle or hazardous machinery, may be impaired for some time after general anesthesia. **Drug Interactions:** The induction dose requirements of DIPRIVAN Injection may be reduced in patients with intramuscular or intravenous premedication, particularly with narcotics (eg, morphine, meperidine, and fentanyl) and combinations of narcotics and sedatives (eg, benzodiazepines, barbiturates, chloral hydrate, droperidol, etc.). These agents may increase the anesthetic effects of DIPRIVAN Injection and may also result in more pronounced decreases in systolic, diastolic, and mean arterial pressures and cardiac output. During maintenance of anesthesia, the rate of DIPRIVAN Injection administration should be adjusted according to the desired level of anesthesia and may be reduced in the presence of supplemental analgesic agents (eg, nitrous oxide or opioids). The concurrent administration of potent inhalational agents (eg, isoflurane, enflurane, and halothane) during maintenance with DIPRIVAN Injection has not been extensively evaluated. These inhalational agents can also be expected to increase the anesthetic and cardiorespiratory effects of DIPRIVAN Injection. DIPRIVAN Injection does not cause a clinically significant change in onset, intensity or duration of action of the commonly used neuromuscular blocking agents (eg, succinylcholine and nondepolarizing muscle relaxants). No significant adverse interactions with commonly used premedications or drugs used during anesthesia (including a range of muscle relaxants, inhalational agents, analgesic agents, and local anesthetic agents) have been observed. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** Animal carcinogenicity studies have not been performed with propofol. In vitro and in vivo animal tests failed to show any potential for mutagenicity by propofol. Tests for mutagenicity included the Ames (using *Salmonella* sp) mutation test, gene mutation/gene conversion using *Saccharomyces cerevisiae*, in vitro cytogenetic studies in Chinese hamsters and a mouse micronucleus test. Studies in female rats at intravenous doses up to 15 mg/kg/day (6 times the maximum recommended human induction dose) for 2 weeks before pregnancy to day 7 of gestation did not show impaired fertility. Male fertility in rats was not affected in a dominant lethal study at intravenous doses up to 15 mg/kg/day for 5 days. **Pregnancy Category B:** Reproduction studies have been performed in rats and rabbits at intravenous doses of 15 mg/kg/day (6 times the recommended human induction dose) and have revealed no evidence of impaired fertility or harm to the fetus due to propofol. Propofol, however, has been shown to cause maternal deaths in rats and rabbits and decreased pup survival during the lactating period in dams treated with 15 mg/kg/day (or 6 times the recommended human induction dose). The pharmacological activity (anesthesia) of the drug on the mother is probably responsible for the adverse effects seen in the offspring. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human responses, this drug should be used during pregnancy only if clearly needed. **Labor and Delivery:** DIPRIVAN Injection is not recommended for obstetrics, including cesarean section deliveries, because there are insufficient data to support its safety to the fetus. **Nursing Mothers:** DIPRIVAN Injection is not recommended for use in nursing mothers because DIPRIVAN Injection has been reported to be excreted in human milk and the effects of oral absorption of small amounts of propofol are not known. **Pediatric Use:** DIPRIVAN Injection is not recommended for use in pediatric patients because safety and effectiveness have not been established. **Neurosurgical Anesthesia:** Studies to date indicate that DIPRIVAN Injection decreases cerebral blood flow, cerebral metabolic oxygen consumption, and intracranial pressure, and increases cerebrovascular resistance. DIPRIVAN Injection does not seem to affect cerebrovascular reactivity to changes in arterial carbon dioxide tension. Despite these findings, DIPRIVAN Injection is not recommended for use at this time in patients with increased intracranial pressure or impaired cerebral circulation because DIPRIVAN Injection may cause substantial decreases in mean arterial pressure, and consequently, substantial decreases in cerebral perfusion pressure. Further studies are needed to substantiate what happens to intracranial pressure following DIPRIVAN Injection when decreases in mean arterial and cerebral perfusion pressures are prevented by appropriate measures. **ADVERSE REACTIONS:** Adverse event information is derived from controlled clinical trials and worldwide marketing experience. In the description below, rates of the more common events represent US/Canadian clinical study results. Less frequent events are derived principally from marketing experience in approximately 7 million patients and from publications; there are insufficient data to support an accurate estimate of their incidence rates. The following estimates of adverse events for DIPRIVAN Injection are derived from reports of 1573 patients included in the US/Canadian induction and maintenance studies. These studies were conducted using a variety of premedications, varying lengths of surgical procedures and various other anesthetic agents. Most adverse events were mild and transient. The following adverse events were reported in patients treated with DIPRIVAN Injection. They are presented within each body system in order of decreasing frequency. **Incidence Greater than 1%—All events regardless of causality, derived from clinical trials. Body as a Whole:** Fever. **Cardiovascular:** Hypotension* (see also CLINICAL PHARMACOLOGY). Bradycardia, Hypertension. **Central Nervous System:** Movement*, Headache, Dizziness, Twitching, Bucking/Jerking/Thrashing, Clonic/Myoclonic Movement. **Digestive:** Nausea*, Vomiting*, Abdominal Cramping. **Injection Site:** Burning/Stinging*, Pain*, Tingling/Numbsness, Coldness. **Respiratory:** Cough, Hiccough, Apnea (see also CLINICAL PHARMACOLOGY). **Skin and Appendages:** Flushing. Incidence of unmarked events is 1%-3%; *3% to 10%; **10% or greater. **Incidence Less than 1%—Causal Relationship Probable** (Adverse events reported only in the literature, not seen in clinical trials, are italicized.) **Body as a Whole:** Extremities Pain, Chest Pain, Neck Stiffness, Trunk Pain. **Cardiovascular:** Tachycardia, Premature Ventricular Contractions, Premature Atrial Contractions, Syncope, Abnormal ECG, ST Segment Depression. **Central Nervous System:** Shivering, Somnolence, Hypertonia/Dystonia, Paresthesia, Tremor, Abnormal Dreams, Agitation, Confusion, Delirium, Euphoria, Fatigue, Moaning, Rigidity. **Digestive:** Hypersalivation, Dry Mouth, Swallowing. **Injection Site:** Discomfort, Phlebitis, Hives/Itching, Redness/

DIPRIVAN[®] (propofol) Injection

Discoloration. **Musculoskeletal:** Myalgia. **Respiratory:** Upper Airway Obstruction, Bronchospasm, Dyspnea, Wheezing, Hypoventilation, Burning in Throat, Sneezing, Tachypnea, Hyperventilation, Hypoxia. **Skin and Appendages:** Rash, Urticaria. **Special Senses:** Amblyopia, Diplopia, Eye Pain, Taste Perversion, Tinnitus. **Urogenital:** Urine Retention, Green Urine. **Incidence Less than 1%—Causal Relationship Unknown** (Adverse events reported only in the literature, not seen in clinical trials, are italicized.) **Cardiovascular:** Arrhythmia, Bigeminy, Edema, Ventricular Fibrillation, Heart Block, Myocardial Ischemia. **Central Nervous System:** Anxiety, Emotional Lability, Depression, Hysteria, Insomnia, Generalized and Localized Seizures, Opisthotonus. **Digestive:** Diarrhea. **Respiratory:** Laryngospasm. **Skin and Appendages:** Diaphoresis, Pruritus, Conjunctival Hyperemia. **Special Senses:** Ear Pain, Nystagmus. **Urogenital:** Abnormal Urine. **DRUG ABUSE AND DEPENDENCE:** None known. **OVERDOSAGE:** To date, there is no known case of acute overdosage, and no specific information on emergency treatment of overdosage is available. If accidental overdosage occurs, DIPRIVAN Injection administration should be discontinued immediately. Overdosage is likely to cause cardiorespiratory depression. Respiratory depression should be treated by artificial ventilation with oxygen. Cardiovascular depression may require repositioning of the patient by raising the patient's legs, increasing the flow rate of intravenous fluids and administering pressor agents and/or anticholinergic agents. The intravenous LD₅₀ values are 53 mg/kg in mice and 42 mg/kg in rats. **DOSAGE AND ADMINISTRATION:** **Induction:** Dosage should be individualized and titrated to the desired effect according to the patient's age and clinical status. Most adult patients under 55 years of age and classified ASA I and II are likely to require 2.0 to 2.5 mg/kg of DIPRIVAN Injection, for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular narcotics. For induction, DIPRIVAN Injection should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. It is important to be familiar and experienced with the intravenous use of DIPRIVAN Injection before treating elderly, debilitated, hypovolemic patients and/or those in ASA Physical Status Classes III or IV. These patients may be more sensitive to the effects of DIPRIVAN Injection; therefore, the dosage of DIPRIVAN Injection should be decreased in these patients by approximately 50% (20 mg every 10 seconds) according to their conditions and responses. (See **PRECAUTIONS**, and **DOSAGE GUIDE**.) Additionally, as with most anesthetic agents, the effects of DIPRIVAN Injection may be increased in patients who have received intravenous sedative or narcotic premedications shortly prior to induction. **Maintenance:** Anesthesia can be maintained by administering DIPRIVAN Injection by infusion or intermittent IV bolus injection. The patient's clinical response will determine the infusion rate or the amount and frequency of incremental injections. When administering DIPRIVAN Injection by infusion, it is recommended that drop counters, syringe pumps or volumetric pumps be used to provide controlled infusion rates. **Continuous Infusion:** DIPRIVAN Injection 0.1 to 0.2 mg/kg/min administered in a variable rate infusion with 60%-70% nitrous oxide and oxygen provides anesthesia for patients undergoing general surgery. Maintenance by infusion of DIPRIVAN Injection should immediately follow the induction dose in order to provide satisfactory or continuous anesthesia during the induction phase. During this initial period following the induction injection higher rates of infusion are generally required (0.15 to 0.20 mg/kg/min) for the first 10 to 15 minutes. Infusion rates should subsequently be decreased by 30%-50% during the first half-hour of maintenance. Changes in vital signs (increases in pulse rate, blood pressure, sweating and/or tearing) that indicate a response to surgical stimulation or lightening of anesthesia may be controlled by the administration of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) incremental boluses and/or by increasing the infusion rate. If vital sign changes are not controlled after a five minute period, other means such as a narcotic, barbiturate, vasodilator or inhalation agent therapy should be initiated to control these responses. For minor surgical procedures (ie, body surface) 60%-70% nitrous oxide can be combined with a variable rate DIPRIVAN Injection infusion to provide satisfactory anesthesia. With more stimulating surgical procedures (ie, intra-abdominal) supplementation with analgesic agents should be considered to provide a satisfactory anesthetic and recovery profile. Infusion rates should always be titrated downward in the absence of clinical signs of light anesthesia until a mild response to surgical stimulation is obtained in order to avoid administration of DIPRIVAN Injection at rates higher than are clinically necessary. Generally, rates of 0.05 to 0.1 mg/kg/min should be achieved during maintenance in order to optimize recovery times. **Intermittent Bolus:** Increments of DIPRIVAN Injection 25 mg (2.5 mL) or 50 mg (5.0 mL) may be administered with nitrous oxide in patients undergoing general surgery. The incremental boluses should be administered when changes in vital signs indicate a response to surgical stimulation or light anesthesia. DIPRIVAN Injection has been used with a variety of agents commonly used in anesthesia such as atropine, scopolamine, glycopyrrolate, diazepam, depolarizing and nondepolarizing muscle relaxants, and narcotic analgesics, as well as with inhalational and regional anesthetic agents. (See **Drug Interactions**.)

DOSAGE GUIDE

INDICATION	DOSAGE AND ADMINISTRATION
Induction	Dosage should be individualized. Adults: Are likely to require 2.0 to 2.5 mg/kg (approximately 40 mg every 10 seconds until induction onset). Elderly, Debilitated, Hypovolemic, and/or ASA III or IV Patients: Are likely to require 1.0 to 1.5 mg/kg (approximately 20 mg every 10 seconds until induction onset).
Maintenance Infusion	Variable rate infusion —titrated to the desired clinical effect. Adults: Generally, 0.1 to 0.2 mg/kg/min (6 to 12 mg/kg/h). Elderly, Debilitated, Hypovolemic and/or ASA III or IV Patients: Generally, 0.05 to 0.1 mg/kg/min (3 to 5 mg/kg/h).
Intermittent Bolus	Increments of 25 mg to 50 mg, as needed.

Compatibility and Stability: DIPRIVAN Injection should not be mixed with other therapeutic agents prior to administration. **Dilution Prior to Administration:** When DIPRIVAN Injection is diluted prior to administration, it should only be diluted with 5% Dextrose Injection, USP, and it should not be diluted to a concentration less than 2 mg/mL because it is an emulsion. In diluted form it has been shown to be more stable when in contact with glass than with plastic (95% potency after 2 hours of running infusion in plastic). **Administration into a Running IV Catheter:** Compatibility of DIPRIVAN Injection with the coadministration of blood/serum/plasma has not been established. (See **WARNINGS**.) DIPRIVAN Injection has been shown to be compatible with the following intravenous fluids when administered into a running IV catheter: 5% Dextrose Injection, USP; Lactated Ringers Injection, USP; Lactated Ringers and 5% Dextrose Injection; 5% Dextrose and 0.45% Sodium Chloride Injection, USP; 5% Dextrose and 0.2% Sodium Chloride Injection, USP. **Handling Procedures:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. DIPRIVAN Injection must not be administered through a microbiological filter because this could restrict the flow of DIPRIVAN and/or cause the breakdown of the emulsion. Do not use if there is evidence of separation of the phases of the emulsion. Strict aseptic techniques must always be maintained during handling as DIPRIVAN Injection is a single-use parenteral product and contains no antimicrobial preservatives. The vehicle is capable of supporting rapid growth of microorganisms. DIPRIVAN Injection should be prepared for use just prior to initiation of each individual anesthetic procedure. DIPRIVAN Injection should be drawn into sterile syringes immediately after ampules or vials are opened. When using vials with volumetric infusion devices insert sterile vent spike through rubber stopper and immediately connect IV line. Administration should commence promptly and be completed within 6 hours after the ampules or vials have been opened. DIPRIVAN Injection should be prepared for single patient use only and any unused portions of DIPRIVAN Injection, reservoirs, IV lines or solutions containing DIPRIVAN Injection must be discarded at the end of the anesthetic procedure. Failure to follow aseptic handling procedures may result in microbial contamination causing fever and/or other adverse consequences which could lead to life-threatening illness. **Aseptic Technique* for Handling DIPRIVAN Injection Ampules:** • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Disinfect neck surface of ampule using 70% isopropyl alcohol. Swab neck of ampule by wiping in one direction and let dry. • Protect fingers and hands by using sterile gauze when opening the ampule. • Withdraw DIPRIVAN Injection into a sterile syringe. • Immediately replace needle cap and discard ampule. • Label syringe with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. **Aseptic Technique* for Handling DIPRIVAN Injection Vials (and for Use With Volumetric Infusion Devices):** • Wear clean garments. • Wash hands and fingernails using an antimicrobial handwash. • When appropriate, wear sterile gloves, mask and hair cover. • Remove metal cap from vial. • Disinfect rubber stopper of vial using 70% isopropyl alcohol. Wipe in one direction and let dry. • Insert sterile vent spike through rubber stopper and remove luer cap. • Connect a sterile syringe(s) to vent spike and withdraw entire contents. (Or when using volumetric infusion devices, aseptically connect IV line to vent spike). • Immediately cap syringe(s) with sterile closure(s) and discard vial and vent spike. • Label syringe(s) (or vial when using volumetric infusion devices) with appropriate information, including date, time and patient name. • Administer promptly. • Discard any unused DIPRIVAN Injection and reservoirs, IV lines, or solutions containing DIPRIVAN Injection at the end of the anesthetic procedure or within 6 hours—whichever occurs sooner. *These techniques are not intended to preempt more stringent, established institutional guidelines for the aseptic handling and administration of sterile parenteral drug products. **HOW SUPPLIED:** DIPRIVAN Injection is available in ready to use 20 mL ampules and 50 mL infusion vials containing 10 mg/mL of propofol. 20 mL ampules (NDC 0038-0290-20) 50 mL infusion vials (NDC 0038-0290-50) Store below 22°C (72°F). Do not store below 4°C (40°F). Refrigeration is not recommended. Protect from light. Shake well before use.

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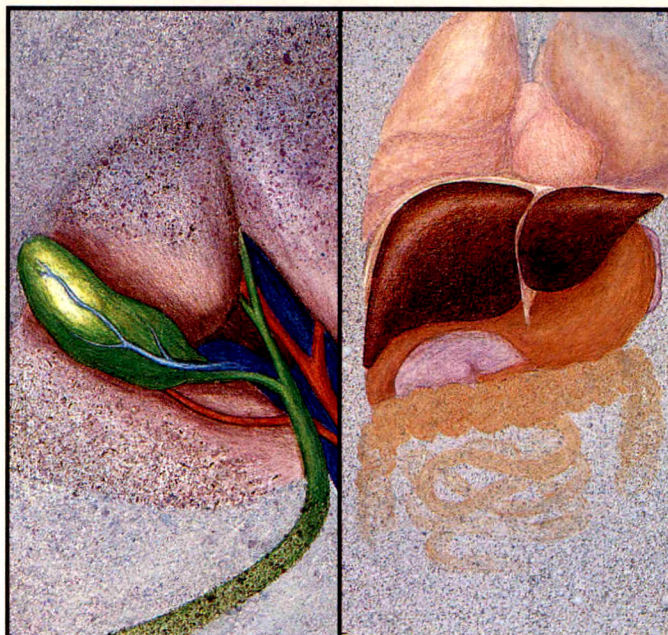
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For more procedures

For more reasons



Cholecystectomy

**Biliary tract
repair**

Common patient type
Obese

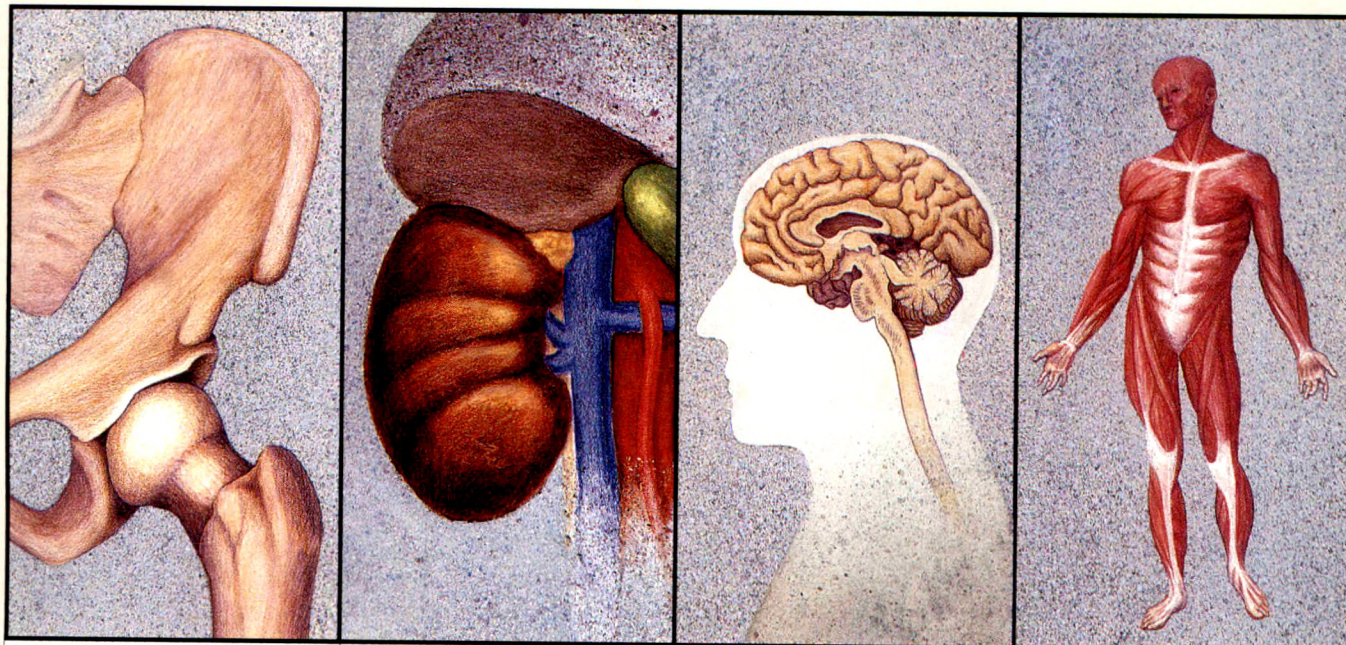
Common patient type
Both adults and
children

Advantage of Tracrium

No difference in recovery from neuromuscular blockade between normal and obese patients. Recovery time with vecuronium can take three times as long in the obese patient.¹

Advantage of Tracrium

Clinical response unaffected by hepatic function² or patient age.³ Duration of action can be prolonged with vecuronium in these patients.⁴



Total hip replacement

Renal surgery

Neurosurgery for trauma

Everyday procedures

Common patient type

Elderly women and men

Common patient type

Both adults and children

Common patient type

Both adults and children

Common patient type

Average

Advantage of Tracrium

Recovery time unaffected by age.³ With vecuronium, recovery time can be twice as long in the elderly.⁵

Advantage of Tracrium

Recovery time unaffected by renal dysfunction.² With vecuronium, recovery time can be prolonged.⁶

Advantage of Tracrium

Effect unchanged by concomitant anticonvulsant medications (phenytoin, carbamazepine).^{7,8} The effect of vecuronium is decreased in patients receiving these agents.^{8,9}

Advantage of Tracrium

The same reasons Tracrium is ideal for special patient types make it the choice for everyday procedures.

TRACRIUM[®] INJECTION

(atracurium besylate) 10 mg/mL

For more predictable recovery

See brief summary of prescribing information on adjacent page.

TRACRIUM® INJECTION (atracurium besylate)

Brief Summary

This drug should be used only by adequately trained individuals familiar with its actions, characteristics, and hazards.

INDICATIONS AND USAGE: Tracrium is indicated, as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS: Tracrium is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS: TRACRIUM SHOULD BE USED ONLY BY THOSE SKILLED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR ENDOTRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. ANTICHOLINERGIC REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. DO NOT GIVE TRACRIUM BY INTRAMUSCULAR ADMINISTRATION. Tracrium has no known effect on consciousness, pain threshold, or cerebation. It should be used only with adequate anesthesia. Tracrium Injection, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. Depending on the resultant pH of such mixtures, Tracrium may be inactivated and a free acid may be precipitated. Tracrium Injection 10 mL multiple dose vials contain benzyl alcohol. Benzyl alcohol has been associated with an increased incidence of neurological and other complications in newborn infants which are sometimes fatal. Tracrium Injection 5 mL ampuls and 5 mL single use vials do not contain benzyl alcohol.

PRECAUTIONS: **General:** Although Tracrium is a less potent histamine releaser than d-tubocurarine or metocurine, the possibility of substantial histamine release in sensitive individuals must be considered. Special caution should be exercised in administering Tracrium to patients in whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) and in patients with any history (e.g., severe anaphylactoid reactions or asthma) suggesting a greater risk of histamine release. In these patients, the recommended initial Tracrium dose is lower (0.3 to 0.4 mg/kg) than for other patients and should be administered slowly or in divided doses over one minute. Since Tracrium has no clinically significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation. As a result, bradycardia during anesthesia may be more common with Tracrium than with other muscle relaxants. Tracrium may have profound effects in patients with myasthenia gravis, Eaton-Lambert syndrome, or other neuromuscular diseases in which potentiation of nondepolarizing agents has been noted. The use of a peripheral nerve stimulator is especially important for assessing neuromuscular blockade in these patients. Similar precautions should be taken in patients with severe electrolyte disorders or carcinomatosis. Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. Reports of MH have been rare in cases in which Tracrium has been used. In studies of MH-susceptible animals (swine) and in a clinical study of MH-susceptible patients, Tracrium did not trigger this syndrome. Resistance to nondepolarizing neuromuscular blocking agents may develop in burn patients. Increased doses of nondepolarizing muscle relaxants may be required in burn patients and are dependent on the time elapsed since the burn injury and the size of the burn. The safety of Tracrium has not been established in patients with bronchial asthma. **Long-Term Use in Intensive Care Unit (ICU):** Tracrium has been used to facilitate mechanical ventilation in ICU patients. When there is a need for long-term mechanical ventilation, the benefits to risk ratio of neuromuscular blockade must be considered. There is only limited information on the efficacy and safety of Tracrium administered by long-term (days to weeks) intravenous infusion to facilitate mechanical ventilation in intensive care facilities. For Tracrium, as with other neuromuscular blocking agents used in intensive care facilities, available evidence suggests that there is wide interpatient variability in dosage requirements and that these requirements may change with time. Limited data suggest that Tracrium infusion requirements may increase with prolonged administration in the ICU. As with other neuromuscular blocking agents, little information is available on the plasma levels or clinical consequences of atracurium metabolites following long-term (days to weeks) infusion of Tracrium in the intensive care unit setting. One metabolite of atracurium, laudanosine, when administered alone to laboratory animals, has been associated with cerebral excitatory effects. Physiological effects of laudanosine in humans have not been demonstrated. The effects of hemodialysis, hemoperfusion and hemofiltration on plasma levels of atracurium and its metabolites are unknown. **Drug Interactions:** Drugs which may enhance neuromuscular blocking action of Tracrium include: enflurane, isoflurane, halothane, certain antibiotics, especially the aminoglycosides and polymyxins; lithium; magnesium salts; procainamide; and quinidine. If other muscle relaxants are used during the same procedure, the possibility of a synergistic or antagonist effect should be considered. The prior administration of succinylcholine does not enhance the duration, but quickens the onset and may increase the depth of neuromuscular blockade induced by Tracrium. Tracrium should not be administered until a patient has recovered from succinylcholine-induced neuromuscular blockade. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** A positive response was observed in the mouse lymphoma assay under conditions which killed over 80% of the treated cells. A far weaker response was observed in the presence of metabolic activation at concentrations which also killed over 80% of the treated cells. **Pregnancy: Teratogenic Effects:** Pregnancy Category C. Tracrium has been shown to be potentially teratogenic in rabbits, when given in doses up to approximately one-half the human dose. There are no adequate and well-controlled studies in pregnant women. Tracrium should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that forceps delivery will be necessary may increase. Tracrium (0.3 mg/kg) has been administered to 26 pregnant women during delivery by cesarean section. No harmful effects were attributable to Tracrium in any of the newborn infants, although small amounts of Tracrium were shown to cross the placental barrier. The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered. In patients receiving magnesium sulfate, the reversal of neuromuscular blockade may be unsatisfactory and Tracrium dose should be lowered as indicated. **Nursing Mothers:** It is not known whether this drug is excreted in human milk. Caution should be exercised when Tracrium is administered to a nursing woman. **Pediatric Use:** Safety and effectiveness in children below the age of 1 month have not been established.

ADVERSE REACTIONS: **Observed in Controlled Clinical Studies:** Tracrium produced few adverse reactions during extensive clinical trials. Most were suggestive of histamine release (see Precautions Section). The overall incidence rate for clinically important adverse reactions was 7/875 or 0.8%. Most adverse reactions were of little clinical significance unless they were associated with significant hemodynamic changes. Substantial vital sign changes greater than or equal to 30% observed in 530 patients, without cardiovascular disease, were as follows: in those patients given the recommended initial dosage range of 0.31 to 0.50 mg/kg of Tracrium, mean arterial pressure increased in 2.8% and decreased in 2.1% of patients while the heart rate increased in 2.8% of these patients. At doses of ≥ 0.60 mg/kg, 14.3% of the studied patients had a decrease in mean arterial pressure while 4.8% had an increase in heart rate. At doses ≤ 0.30 mg/kg, mean arterial pressure increased in 1.9% and decreased in 1.1% of patients, while heart rate increased in 1.6% and decreased in 0.8% of these patients. **Observed in Clinical Practice:** Based on clinical experience in the U.S. and the United Kingdom of approximately 3 million patients given Tracrium the following adverse reactions are among the most frequently reported: **General:** allergic reactions (anaphylactoid or anaphylactoid) which, in rare instances, were severe (e.g., cardiac arrest); **Musculoskeletal:** inadequate, prolonged block; **Cardiovascular:** hypotension, vasodilatation (flushing), tachycardia, bradycardia; **Respiratory:** dyspnea, bronchospasm, laryngospasm; **Integumentary:** rash, urticaria, injection site reaction.

STORAGE: Tracrium Injection should be refrigerated at 2° to 8°C (36° to 46°F) to preserve potency. DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use Tracrium Injection within 14 days even if refrigerated.

1. Weinstein JA, Matteo RS, Ornstein E, Schwartz A, Goldstoft M, Thal G. Pharmacodynamics of vecuronium and atracurium in the obese surgical patient. *Anesth Analg*. 1988;67:1149-1153. 2. Ward S, Neill EAM. Pharmacokinetics of atracurium in patients in acute hepatic failure (with acute renal failure). *Br J Anaesth*. 1983;55:1169-1172. 3. d'Hollander A, Luyckx C, Barvais L, DeVille A. Clinical evaluation of atracurium besylate requirement for a stable muscle relaxation during surgery: lack of age-related effects. *Anesthesiology*. 1983;39:237-240. 4. Lebrault C, Duvaldestin P, Henzel D, Chauvin M. Gueshon P. Pharmacokinetics and pharmacodynamics of vecuronium in patients with cholestasis. *Br J Anaesth*. 1986;58:963-987. 5. d'Hollander A, Massaux F, Nevelsteen M, Agoston S. Age-dependent dose-response relationship of Org NC45 in anaesthetized patients. *Br J Anaesth*. 1982;54:653-657. 6. Lynam DP, Cronnelly R, Castagnoli KP, et al. The pharmacodynamics and pharmacokinetics of vecuronium in patients anesthetized with isoflurane with normal renal function or with renal failure. *Anesthesiology*. 1988;69:227-231. 7. Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL, Diaz J. Chronic phenytoin therapy and nondepolarizing muscular blockade. *Anesthesiology*. 1985;63:A331. Abstract. 8. Ebrahimi Z, Bulkey R, Roth S. Carbamazepine therapy and neuromuscular blockade with atracurium and vecuronium. *Anesth Analg*. 1988;67:S55. Abstract. 9. Ornstein E, Matteo RS, Silverberg PA, Schwartz AE, Young WL. Dose-response relationship for vecuronium in the presence of chronic phenytoin therapy. *Anesth Analg*. 1986;65:S116. Abstract.

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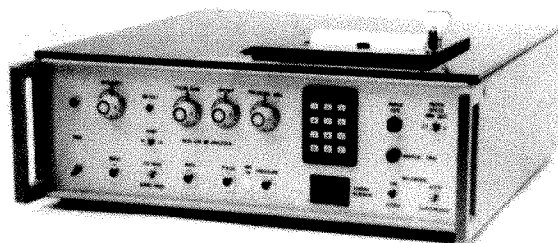
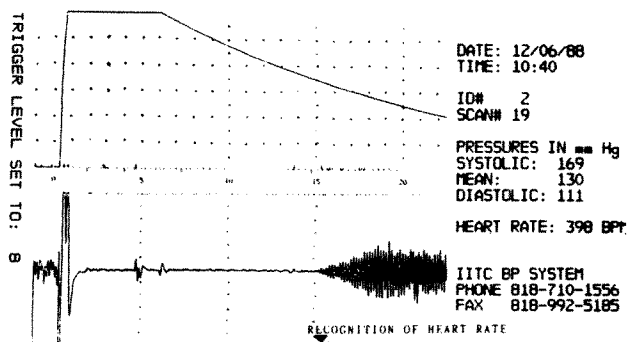
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Electrical Shock by Dislodged Spark Gap in Bipolar Electrosurgical Device

Timothy B. Gilbert, MD, Michael Shaffer, DSc, and Marianne Matthews, MD

Department of Anesthesiology, George Washington University Medical Center, Washington, D.C.

Despite the advent of specialized power distribution systems and electrical safety monitors, the risk of electrical shock and injury still exists in the modern operating room. Electrosurgical devices—despite a more than 60-yr history of use and development—increase the number and complexity of potential hazards to patients (1). We report a case in which a faulty electrosurgical device attached to a patient caused a severe shock to an anesthesia resident who completed an electrical circuit through ground. Before the shock, properly working safety equipment was unable to detect the existence of a hazardous equipment failure. In this particular case, the responsibility for the incident originated with a ground fault in a bipolar coagulator having its own isolated power supply.

Case Report

A 57-yr-old male patient was placed in the sitting position under general anesthesia for an intracranial procedure. Perioperative monitors included an electrocardiogram, a peripherally placed central venous pressure monitor, a neuromuscular stimulator, a bladder temperature probe, and an intraarterial blood pressure monitor. After uneventful incision of the scalp, the neurosurgeon used a Codman Malis model NS237 bipolar coagulator at a power setting of 35 (equivalent to 8.4 ± 1.7 W) to coagulate vessels. He initially complained of "lack of power" in coagulation and the presence of scalp muscle contraction away from the bipolar tips. The anesthesia resident was requested to check the depth of neuromuscular paralysis. Grasping the patient's hand, she simultaneously contacted a steel rod attached to the operating table frame. As the coagulator was activated, she suffered a shock severe enough to thrust her several feet into the adjacent anesthesia machine. The line

isolation monitor did not alarm (later determined to be properly operating), nor did the coagulator main fuse or line circuit breaker trip. Although the resident suffered a second-degree burn and ecchymosis in that arm, she recovered without sequelae. No adverse effects could be found in the anesthetized patient.

Within this bipolar unit is an inductive/capacitive oscillatory circuit that is discharged by a pair of spark gaps, creating a high-frequency waveform for coagulating tissues. A simplified schematic diagram shown in Figure 1 details the normal configuration, which includes the oscillatory circuit and three isolation transformers (denoted T1–3).

An internal inspection of the coagulator revealed the spark gap assembly to be dislodged (Figure 2B) with both of its ceramic insulator mounts fractured (Figure 2A), apparently because of previously being dropped. The metal bar of the spark gap assembly had fallen near the secondary coil of the variable-output transformer, resulting in the creation of a new spark gap (Figure 2C). The resultant high-frequency output of the unit was no longer isolated from, but connected to, ground through T3, whereby a current path was set up through the patient and resident to ground and back to the coagulator (Figure 3).

Measurements made in the George Washington University Bioelectronics Laboratory confirmed the shock hazard. After placing a 50- Ω resistive load on the output jacks (the standard test load designated by the manufacturer for measuring output), four different scenarios were tested: with the (a) coagulator properly assembled, (b) dislodged spark gap contacting the chassis ground, (c) dislodged spark gap contacting the output transformer, and (d) dislodged spark gap near (3 mm) but not contacting the output transformer, creating a new spark gap. Current output measurements are shown in Table 1, and the substantial shock hazard available with the dislodged spark gap is noted. Fortunately, the actual series resistance of the patient, resident's arm, operating room table, and floor was estimated to far exceed the 50- Ω test load, attenuating the electrical injury to the resident.

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Address correspondence to Dr. Gilbert, Department of Anesthesiology, George Washington University Medical Center, 4th Floor, Room 4250, 901 23rd Street, NW, Washington, DC 20037.

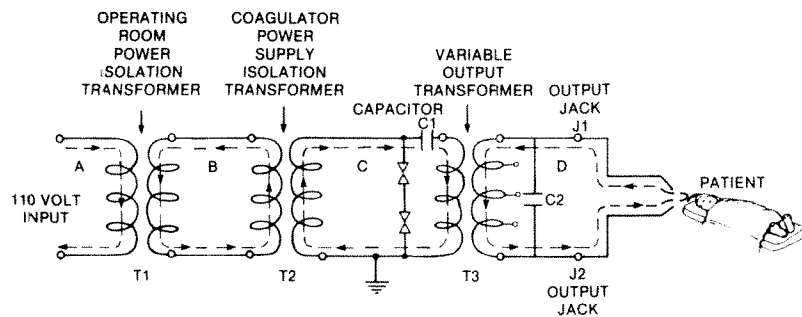


Figure 1. Proper current flow from power source to the bipolar coagulator to the patient is shown (dashed lines). Spark gaps are denoted by triangles. Isolation is maintained and current is transferred within loops A-D by the mutual inductance of transformers T1-3.

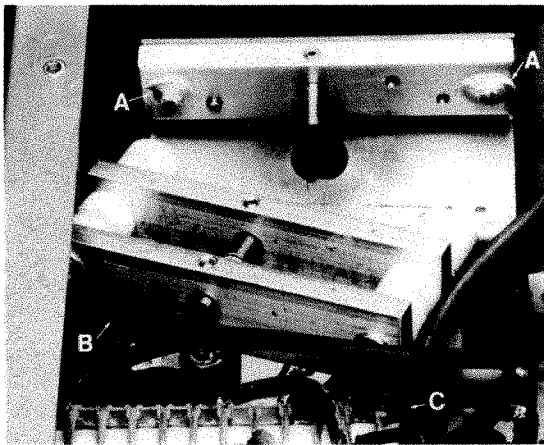


Figure 2. Fractured ceramic mounts (A) and partially dislodged spark-gap assembly (B) in the bipolar coagulator create a new spark gap and isolated pathway for high-frequency current across to the transformer coil (C).

Discussion

Electrical safety monitors, such as line isolation monitors (LIM) and ground fault interruptors, are designed to detect abnormal equipment leakage currents to ground, primarily of low frequencies (typically 60 Hz). They may not detect leakage currents from equipment with broken ground connections or from equipment such as electrosurgical devices that generate higher (typically 0.3–2.0 MHz) frequency currents (2).

The LIM can only test if the secondary of the operating room isolation transformer power supply is isolated. Manufacturers of electrical equipment often have placed separate isolation transformers within the power supply of their products; the LIM is then insensitive to ground faults distal to this second level of isolation. This incident points out that the use of a second level of isolation eliminates the safety provided by an LIM monitoring the first level of isolation. Perhaps manufacturers who use isolation transformers within their equipment should have separate alarm lights to show that their isolation is being maintained. In general, isolation transformers and

their LIMs are anachronistic, being still required by the National Fire Protection Association in only one circumstance—when explosive anesthetics are used. Clearly the present hazardous situation is not restricted to the operating room but could have occurred in other hospital locations not equipped with isolation transformers and LIMs.

Most reports of electrosurgery-related injury involve monopolar devices, usually with faulty ground pad function (3) that allows a high-density current to exit the skin at alternative grounds (e.g., unisolated electrocardiographic leads [4], Doppler probe [5], or temperature probes [6,7]). Bipolar devices are usually considered to be particularly safe with respect to such ground faults and are often preferred over unipolar devices in situations when limiting current flow is desired or necessary (for example, in intracranial or Fallopian tube surgery, or in patients with pacemakers where the electrosurgical effect is confined to those tissues in direct contact with the hand-held tips) (2).

Spark gaps can form anywhere electrical components reside close enough for high-frequency current to traverse, as is the case here. It was serendipitous that the partially broken spark gap had fallen in such a way as to connect the secondary coil of the isolation transformer to ground, without concurrently shorting the primary coil to ground. Without both conditions, the injury could not have occurred.

In retrospect, an equipment malfunction might have been suspected when the surgeon noted excessive local muscle contraction and decreased coagulation action at the bipolar site, indicating current flow beyond the bipolar tip return (i.e., acting like a monopolar device). This also supports Aronow and Bruner's (1) view that careful investigation of an electrosurgery-associated injury usually reveals a gross instrument fault or neglect of proper procedure. Guidelines for preventing electrosurgery-associated injuries have been published previously (7,8); however, these focus primarily on monopolar devices with ground plate returns. We offer the following additional suggestions for the use of bipolar electrosurgical devices:

Figure 3. Formation of a new spark gap (triangles) across the variable output transformer creates a low-impedance pathway (dashed lines) through the patient, anesthesia resident, and ground, resulting in electrical injury. Notice that the line isolation monitor is insensitive to ground fault occurring distally.

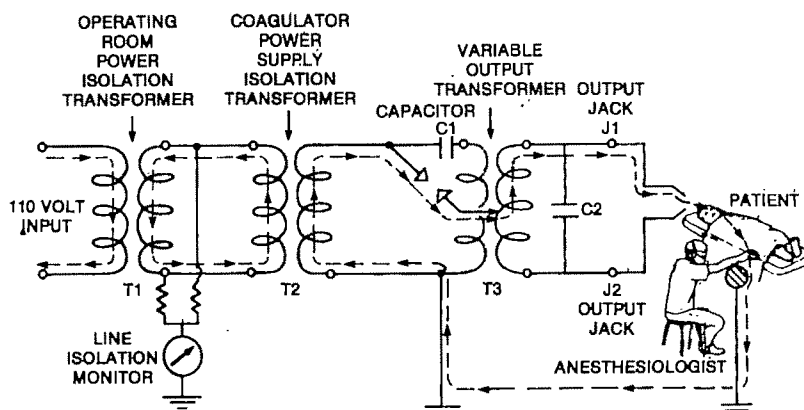


Table 1. Current Output Measurements

	RF current output (A) between:	
	J1 and J2	J1 or J2 and ground
Coagulator properly assembled with output set at 35	0.43	0.00
Spark gap dislodged		
With assembly contacting chassis ground	0.18	0.00
With assembly contacting secondary of transformer T3	0.00	0.00
With assembly near but not contacting secondary of transformer T3	0.00	0.90

1. Inspect the exterior of the electrosurgical device for evidence of damage. Coagulators, because of their small size relative to monopolar devices, are both easier to inspect and more readily dropped or improperly handled.
2. Owing to their size again, coagulators should be rotated gently to detect the "rattle" of internally dislodged parts.
3. Some electrosurgery devices provide an output test socket for detecting proper operation of the active and inactive electrodes; therefore, if so equipped, the device should be tested before use.
4. If during use of the electrosurgical device either excessive muscle contraction away from the electrodes is noted or decreased output occurs, the unit should be removed from service for further inspection.
5. Again owing to their size, coagulators are often

improperly placed; for example, the floor should be avoided because it may be a potentially wet location. Whatever location is chosen, the unit should be secured to prevent damage from falling.

6. These coagulators often denote output power on a numbered, unitless scale; therefore, one should refer to the device's technical manual to determine actual output wattage and current.
7. The average anesthesiologist should take a "black box" approach to any suspiciously acting bipolar instrument, immediately remove it from service, and refer definitive testing and/or repair to appropriately trained technicians.

The authors thank Herbert Grassel of the Bioelectronics Laboratory for obtaining the electrical measurements on the faulty bipolar unit and identifying the cause of the incident.

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Letters to the Editor

Is Hypoxic Pulmonary Vasoconstriction Exaggerated During One-Lung Ventilation in Patients With Patent Ductus Arteriosus?

To the Editor:

We read with interest the recently published clinical report by Baraka et al. (1). Although we were fascinated by their observation, we are disturbed by a potentially serious flaw in the deduction of their final conclusion. Without properly addressing certain physiologic variables (as discussed in the following paragraphs), the conclusion that "(less pulmonary shunt is) . . . attributed to an exaggerated HPV response in these patients" is simply inadequate.

When a patient is placed in the lateral decubitus position, the three zones of pulmonary blood flow distribution, as dictated by gravity, are determined by pulmonary arterial pressure (2). In zone 3, with both transmural pulmonary arterial pressure and transmural pulmonary venous pressure higher than the alveolar pressure, the lung units receive the most pulmonary blood flow. On the other hand, in zone 1, where alveolar pressure is higher than both transmural pulmonary arterial pressure and transmural pulmonary venous pressure, the lung units receive the least blood flow (3). The dependent lung, with most of its units situated in zone 3, will receive more pulmonary blood flow than the nondependent lung, which has most of the units situated in zone 1. Decreasing the pulmonary arterial pressure will cause expansion of zone 1 and contraction of zone 3. Pulmonary arterial pressure must be controlled when evaluating hypoxic pulmonary vasoconstriction.

The cardiac catheterization measurement of patient 1 revealed a right ventricular pressure of 35/0–1 mm Hg with a pulmonary artery pressure of 21/4 mm Hg. Similarly, in patient 2, the catheterization measurement revealed a right ventricular pressure of 50/20 mm Hg and pulmonary arterial pressure of 36/12 mm Hg. In both cases, there existed a 14-mm Hg systolic pressure gradient across the pulmonic valve. Without aortic blood flow through a patent ductus arteriosus, the pressure gradient across the pulmonary valve can only be higher. The existence of this gradient indicated that both patients have subclinical pulmonary valvular stenosis. In otherwise normal patients, the closure of patent ductus arteriosus will cause a decrease in pulmonary arterial pressure. In patients with pulmonary stenosis, the closure of a patent ductus arteriosus could cause an even more significant decrease in pulmonary arterial pressure. In the face of a changing pulmonary arterial pressure, it is unreasonable to assume that the amount of hypoxic pulmonary vasoconstriction can be quantitated with any degree of certainty.

In conclusion, as a result of surgical closure of the patent ductus arteriosus, we would expect to see an increased proportion of pulmonary blood flow to the dependent lung. This redistribution of pulmonary blood flow will be even more pronounced in patients with concomitant pulmonary stenosis. The quantitation of hypoxic pulmonary vasoconstriction in this situation is not possible without quantitating the exact change in pulmonary arterial pressure.

Y. James Kao, MD, PhD
Richard G. Norton, MD
Samuel Kleinman, MD
*Department of Anesthesiology
Texas Tech University Health Sciences Center
Lubbock, TX 79430*

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In Response:

Dr. Kao and colleagues conclude that surgical closure of the patent ductus arteriosus would result in an increased proportion of pulmonary blood flow to the dependent lung, which could explain our finding that the PO_2 during one-lung ventilation in patients with patent ductus arteriosus is higher than expected. However, our report shows that the high PO_2 was observed during one-lung ventilation in patients with patent ductus arteriosus both before and after surgical closure of the patent ductus arteriosus.

Anis Baraka, MD
*Department of Anesthesiology
American University of Beirut
Beirut, Lebanon*

Buzz 'Em or Burn 'Em

To the Editor:

This is a response to the clinical report by Bailey et al. (1) dealing with "electrocautery-induced" airway fire during tracheostomy.

Clearly from the detailed description of the unfortunate incident, an electrocautery device was not involved; rather, an electrosurgical unit or ESU was used. The difference in equipment is profound. An electrocautery device is similar to a soldering iron—it incorporates an electrically heated element. If this component contacts tissue, burning and coagulation result. Heat is transferred from the element to the tissue. No current flows through the body.

By contrast, an electrosurgical generator produces alternating current in the radio-frequency range. This current flows through the body tissue between the active and dispersive electrodes. The current's density and hence its effect is greatest at the point where the active electrode (held by the surgeon) contacts the tissue. Heat is not transferred into the tissue by conduction; it actually arises within the tissue as a result of current flowing through it.

Confusion of the terms "electrosurgery" and "electrocautery" is quite common. Precise description is, however, especially important with the increasing appearance in the operating room of the disposable battery-powered hot wire cautery. This is a veritable cautery unit in contrast to the ESU or "Bovie."

By not understanding the simple distinction, we risk becoming not the Sorcerer but the Sorcerer's Apprentice, and are not in command of our own magic!

Sanford L. Klein, DDS, MD
Department of Anesthesiology
Robert Wood Johnson Medical School
One Robert Place, CN 19
New Brunswick, NJ 08903-0019

Paul F. Leonard, MD
Department of Anesthesiology
Mayo Clinic
200 First Street SW
Rochester, MN 55905

Reference

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Propofol and Malignant Hyperthermia

To the Editor:

A recent letter by Gallen (1) discussed the use of propofol in a possibly malignant hyperthermia-susceptible (MHS) patient. Several points are raised by this brief report.

Gallen states that the use of propofol in MHS patients has not been reported previously. In fact, several case reports have already appeared in the literature (2-4). Two studies have also demonstrated no malignant hyperthermia-triggering effect by propofol in MHS swine (5,6). Propofol does not appear to induce contractures in vitro in skeletal muscle from MHS humans or swine (7). This combination of evidence supports the conclusion that propofol is safe to use in MHS patients.

Since its release in Canada in November 1990, we have used propofol as the primary anesthetic agent in three biopsy-proven MHS patients. Propofol infusions were used for 1-5 h in combination with nitrous oxide, alfentanil, and vecuronium or atracurium. No adverse effects were noted.

In his letter, Gallen states that surgery was attempted using an ester local anesthetic. Is he implying that amide local anesthetics are not safe to use in MHS patients? Although dentists are sometimes reluctant to use amide local anesthetics in MHS patients (8), so are some anesthesiologists. Since 1985, the Malignant Hyperthermia Association

of the United States has advised clinicians that amide local anesthetics are safe to use in MHS patients (9). This view is supported by clinical experience (10), by a large survey of dental anesthesia in MHS patients (11), and by in vivo challenge studies in MHS swine (12,13). All readers should be reminded of their safety.

Gregory Allen, MD, FRCPC
Department of Anesthesia
Ottawa Civic Hospital
1053 Carling Avenue
Ottawa, Ontario K1Y4E9
Canada

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Foreign Body From a Patil-Syracuse Mask

To the Editor:

The Patil-Syracuse mask permits simultaneous ventilation, endoscopy, and endotracheal intubation. The bronchoscope and endotracheal tube are passed through a second opening, which is covered by a diaphragm and can be capped. It is a valuable tool allowing tracheal intubation when a patient can be ventilated but the trachea cannot be intubated. We describe a case in which rupture of the diaphragm created a foreign body that could have been lost within the patient's airway.

A 61-yr-old, 95-kg woman was scheduled for a right modified radical mastectomy for multifocal intraductal car-

The views expressed in this letter are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of the Air Force, Department of Defense, nor the United States Government.

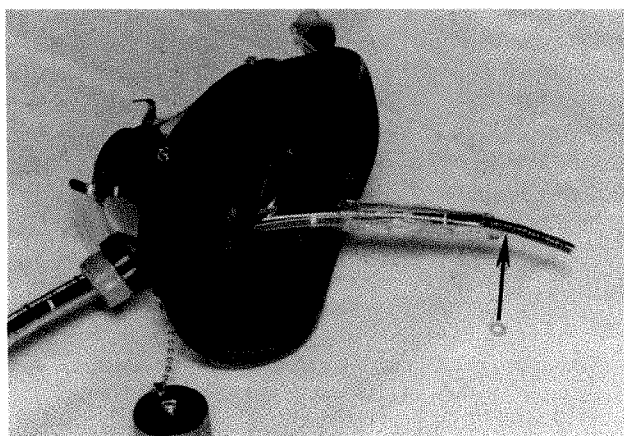


Figure 1. Patil-Syracuse mask showing bronchoscope, endotracheal tube, and fragment of diaphragm. The arrow indicates the position of the fragment on the bronchoscope.

cinoma. Her history was significant for obesity and showed no known complications from a general anesthetic given 12 yr previously. On physical examination, she had full range of motion of her neck and jaw and her tonsillar pillars could be seen.

After induction of general anesthesia with intravenous thiopental and fentanyl, she was easily ventilated via mask. Intravenous vecuronium was given to facilitate tracheal intubation. Her larynx could not be visualized during laryngoscopy. Multiple blades, head positions, and an Endotrol endotracheal tube (Mallinckrodt Critical Care, Glens Falls, N.Y.) were tried. Twice, the endotracheal tube was believed to be at the vocal cords but would not pass. No blind attempts were made to decrease the risk of airway trauma. An attempt to intubate the trachea was made using a Patil-Syracuse mask (Anesthesia Associates, San Marcos, Calif.). After the bronchoscope and 7-mm endotracheal tube were passed through the diaphragm, a significant leak was noted during ventilation. Inspection of the mask and bronchoscope revealed that the diaphragm had been ruptured and a small ring-shaped fragment of it was on the bronchoscope (Figure 1). The diaphragm was changed and tracheal intubation was accomplished on the second attempt. The second diaphragm developed a tear but did not completely rupture. No trauma to the vocal cords was noted during fiberoptic tracheal intubation. The remainder of her anesthetic was uneventful, her trachea was extubated fully awake, and she was informed of the difficulties encountered during her anesthetic.

If the mask air leak had not been noted, this foreign body would have been left in the patient's airway. The position of the fragment was such that the endotracheal tube would have pushed it off the bronchoscope during endotracheal tube placement. A 7-mm endotracheal tube was used in this patient. A larger endotracheal tube might not have made a similar, noticeable leak. A radiograph of the fragment was obtained and it is radiolucent. Other diaphragms were inspected and the material was found to be very thin and easily torn. Operator error was believed not to be a factor as the patient was stable and an adequate amount of time was available to set up the equipment.

We believe that the Patil-Syracuse mask is a valuable tracheal intubation aid. However, care must be taken not to tear the diaphragm during endotracheal tube placement. The diaphragm should be redesigned using a more substantial material to prevent this potential complication.

Laura Williams, LCDR, MC, USNR

National Naval Medical Center

Bethesda, MD 20889-5000

and

Malcolm Grow Air Force Medical Center

Andrews AFB, MD 20331

Paul D. Teague, LCDR, MC, USNR

National Naval Medical Center

Ali H. Nagia, COL, USAF, MC, FS

Malcolm Grow Air Force Medical Center

Do You Think You Could Make Yourself Vomit?

To the Editor:

There is in anesthesia, no stomach like an empty stomach! Obstetric anesthesia, a hazardous procedure because of the ever present risk of aspiration of gastric contents, is rendered even more so if the patient has recently eaten a full meal. A stomach washout or apomorphine injected intravenously to induce vomiting are two methods for emptying a full stomach in this situation. Neither of these is particularly pleasant, although in one study, intravenous apomorphine was preferred by most pregnant women to the use of a stomach tube (1).

A 31-yr-old woman of 27-week gestation was admitted to the delivery suite with bleeding per vaginum. An ultrasound scan showed oligohydramnios and a retroplacental clot. Deterioration of the fetal heart rate on the external cardiotocograph trace resulted in a decision to deliver the fetus by cesarean section. Preparation for anesthesia, however, was complicated by the fact that the patient had eaten a full meal of fish, chips (fries), and dessert an hour before the decision to operate.

The anesthetic assessment proved illuminating. During explanation of the risks of a full stomach and discussion of the methods of emptying it, the reassuring response was, "Don't worry doctor, I can make myself sick (vomit) if you want me to!" This generous offer was gratefully accepted, and 5 min and two kidney basins later, the supper eaten earlier was proudly displayed to an incredulous audience. At no time was digital stimulation of the oropharynx used and the patient quite literally "thought" herself sick.

After administration of 30 mL of 0.3 M sodium citrate, anesthesia was induced and completed uneventfully. A minimal quantity of fluid with virtually no solid or obvious food particles was aspirated from the stomach while the patient was asleep. When seen after the operation, and confirmed again later, the patient confessed to being partly motivated by the fear of "being sick and choking on it." The part she had played in the management of her anesthesia provided her immense satisfaction.

Interestingly, hypnosis has been used to prevent or treat the opposite condition, hyperemesis gravidarum, in obstet-

rics (2). It is also known that gastrointestinal motility may be influenced by hypnotic suggestion (3); but that this may be an instance of self-hypnosis or a related phenomenon like autosuggestion—the implanting of an idea in oneself by oneself—must remain conjectural.

However, this report does demonstrate the value of a frank discussion of anesthetic problems and treatment options, which may unexpectedly provide interesting solutions. In addition to the routine preoperative, "Do you feel sick after an anesthetic?" in similar situations in the future, the suggestion, "Do you think you could make yourself vomit?" may now merit a place in anesthetic practice and should be considered as a simpler alternative to apomorphine or stomach tubes.

D. Suresh, DA, FFARCSI
Department of Anesthesiology
Duke University Medical Center
Box 3094
Durham, NC 27710

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A Method for Withholding Sedatives From Patients Before Obtaining Surgical Consent

To the Editor:

In our busy outpatient surgery department, we have cared for many nervous patients who were given sedatives as soon as their intravenous infusions were started only to discover that they had not yet signed their surgical consent forms. Our desire to withhold such medications before this document was completed led us to devise a sign (see Figure 1) that was



Figure 1.

placed on the intravenous pole of the patient's stretcher. This clearly indicated to all personnel the need to obtain a signed consent before administering sedatives. The use of this sign has eliminated the problem of obtaining consent from sedated patients at our institution.

Mitchel B. Sosis, MD, PhD
Burton Braverman, PhD
Anthony D. Ivankovich, MD
Department of Anesthesiology
Rush-Presbyterian-St. Luke's Medical Center
1753 West Congress Parkway
Chicago, IL 60612

Masseter Muscle Spasm in Children

To the Editor:

Littleford and colleagues (1) have raised provocative, challenging, and clinically important questions in their article on masseter muscle spasm (MMS).

To discuss thoroughly the issues they raise would require more space than a letter to the editor permits. We will therefore limit our comments to the most important findings.

First, Littleford et al. confirm that MMS occurs not infrequently in children (0.3% of inhalation agents in which succinylcholine was used—somewhat lower than that of the several studies demonstrating 1% incidence of MMS in such circumstances).

They also demonstrate that in 61 patients with MMS, there was "no long-term morbidity and no mortality" when the anesthetic was continued with an inhalation agent for a mean duration of 1.5 h. However, in four patients, the anesthetic was aborted; and in four others, the anesthetic was switched to a nontriggering technique.

Littleford et al. separate the patients with MMS into two groups—those experiencing generalized rigidity (chest and limbs) and those experiencing isolated MMS only. They imply that generalized rigidity is more ominous than isolated rigidity. Indeed, the eight children whose anesthetic was stopped or switched belonged to the generalized rigidity group. Hackl et al. (2) and Larach et al. (3) have also suggested that generalized rigidity is more often associated with malignant hyperthermia (MH) susceptibility. Therefore, they conclude that "... anesthesia can be continued safely in cases of isolated MMS when careful monitoring accompanies diagnostic evaluation." What is their advice regarding patients experiencing generalized rigidity?

How too can they be secure in the separation of the two groups? In the pressure of the moment, how can we be sure that the clinician was able to detect limb and/or chest rigidity? Five of the 11 children with generalized rigidity had neuromuscular or skeletal abnormalities, which means that at least some degree of rigidity was present *before* the administration of the anesthetic.

Although postoperative creatine kinase was higher in the generalized rigidity group, there was an overlap between the two groups as there was in the serum potassium values. There was no difference between the groups in carbon dioxide tension, pH, arrhythmias, temperature, and

myoglobin in the urine or serum—values more rapidly available than creatine kinase. In other words, the differences between the groups might be more apparent than real. If they imply that after generalized rigidity the anesthesia management should be different than after isolated rigidity, they are on shaky grounds in separating the groups.

Another significant problem in the paper is a failure of the authors to define MH. They evidently feel that metabolic and respiratory acidosis (pH as low as 7.12), hyperkalemia, rhabdomyolysis, arrhythmias, hyperthermia, along with muscle rigidity (all of which occurred in some cases in both groups) do not represent MH. What is their definition of MH? Fever of 40°C? Sustained rigidity? Death? Indeed, what is the incidence of MH in their institution?

Based on the data they present, we believe that a significant percentage of the patients that developed either isolated or generalized MMS *did* experience MH. In fact, in four instances, clinicians were so convinced that they administered dantrolene.

What we have learned over the past 20 yr is that fever is a late sign of MH, the syndrome may take several hours of anesthetic exposure to develop, and that not all cases of MH are fulminant. The fulminant case is the tip of the iceberg.

Muscle biopsy with halothane and caffeine contracture testing is the most widely accepted way to determine MH susceptibility after questionable signs of MH. Winnipeg is a diagnostic center for MH. Why were biopsy results not reported?

Even leaving aside the controversial issue of the reported high percentage of biopsies positive for MH after MMS, the clinical literature contains *many* case reports of fulminant MH, sometimes leading to death, if inhalation anesthetic agents are continued after MMS (4-8). In at least four of the patients presented by Littleford et al., dantrolene was used and the anesthetic stopped. Perhaps in other patients subtle modifications of the anesthetic occurred such as reduction of inhaled concentration, discontinuation of the inhalation agent midway in the administration of anesthetic, thereby lessening the likelihood of fulminant MH; or perhaps it was luck that none of these patients experienced fulminant MH. Certainly good medical management prevented renal damage after the many instances of myoglobinuria and acidosis.

Given the undeniable evidence that fulminant MH will develop in some patients (perhaps to the authors, the only true form of MH) after MMS and that cardiac arrest will develop in others and they will be found to have Duchenne dystrophy after MMS (6), the logic of continuing anesthesia with a known trigger for MH when there are alternative nontrigger agents available escapes us. To us, this procedure puts convenience ahead of safety.

We urge clinicians to disregard the advice that trigger anesthetic agents for MH be continued after MMS even with end-tidal CO₂ and with arterial blood gas monitoring. Our concern is that once end-tidal CO₂ begins to rise dramatically and the diagnosis of MH is made, the delay in mixing and in administering dantrolene in sufficient quantities will produce injury or death. Although the chances of

this happening are small, why court the risk? Even one preventable death is too many.

What should be done after MMS in an elective procedure? Stop, evaluate the extent of myoglobinuria and hyperkalemia, rule out unsuspected neuromuscular disease, observe for fulminant MH, consider muscle biopsy, and come back another day.

We believe that Littleford's paper will arouse great interest and debate. We hope that their 69th or 70th case of MMS does not prove what has been shown already, both in the peer-reviewed literature and through the MHAUS hotline, that MMS precedes MH in some patients and that even in 1991, MH may be fatal.

Henry Rosenberg, MD
Department of Anesthesiology

John G. Shutack, DO
Departments of Anesthesiology and Pediatrics
Hahnemann University
Broad and Vine
Philadelphia, PA 19102

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In Response:

The letter of Drs. Rosenberg and Shutack indicates that there are differences of opinion regarding the interpretation of the significance of isolated MMS.

Our paper analyzes "our experience in all cases of masseter spasm identified during a 10-yr period, concentrating on the outcome of children who developed isolated MMS and in whom the same anesthetic was continued" (1). Our practice was established before the publication in 1978 of a paper suggesting the possible relationship between MMS and MH (2). Since then, there have been numerous papers on MMS and on its significance or lack of it, which have perpetuated the diagnostic predicament. Based on our experience dating from the 1960s that episodes of isolated MMS after administration of halothane and succinylcholine did not progress to a state of fulminant hypermetabolism, we believed that the continuation of triggering agents was not unsafe. Therefore, our decision not to discontinue triggering agents while surgery proceeded was not based on convenience, as stated by Drs. Rosenberg and Shutack. On the contrary, the degree of vigilance in managing these patients was further heightened.

The key to the clinical diagnosis of MH is the ongoing evidence of hypermetabolism reflected in symptoms or signs that are extraordinary for that patient and procedure (3). Indeed, the earliest sign is a rapidly increasing end-expiratory CO₂ concentration despite seemingly adequate ventilation. Most other signs are secondary and related to sympathetic stimulation (4) and are therefore less reliable.

Several of the metabolic changes appearing early during an MH reaction occur in other pathological states. These are also observed in normal children during halothane anesthesia. In our experience, random samples of capillary blood gases frequently show base deficits of -6 to -10 in fasting pediatric patients and CO₂ tensions of 60-70 mm Hg in spontaneously breathing patients. In addition, a pH range of 7.14-7.24 is not uncommon in these patients. When MMS occurs, there is increased vigor in searching for and recording the signs and laboratory data suggestive of hypermetabolism. It is possible that a prospective study comparing matched groups of anesthetized children (those with MMS and those without) would show parallel changes in pH, body temperature, and incidence of arrhythmias during halothane and succinylcholine administration. Such a study is presently lacking. It may be that the significance of the laboratory findings in patients with isolated MMS is overstated.

Our clinical observations and laboratory data were collected by the same group of anesthesiologists from a single community-based hospital population. One would expect the quality and quantity of data to be less variable than those reported by other investigators with a wide referral base.

Contrary to the reservations of Drs. Rosenberg and Shutack, it was possible for us to clearly identify patients who developed rigidity of other muscle groups besides the masseter muscle. Generalized rigidity has proven to be of greater prognostic value than other adverse anesthetic reactions known to be associated with MH (5,6). Our current practice in cases where generalized rigidity accompanies MMS is to treat the patient according to the Malignant Hyperthermia Association of United States (MHAUS) protocol. Our incidence of MH using generalized rigidity as a criterion was 11 of 42,000 cases over the 10-yr study period.

The results of our muscle biopsies, to be submitted for publication, are similar to those previously reported by Dr. Rosenberg. These results were not included with the paper under discussion as all of the patients had not been tested at the time of submission of the manuscript. Drs. Rosenberg and Shutack state that "muscle biopsy with halothane and caffeine contracture testing is the most widely accepted way to determine MH susceptibility after questionable signs of MH." This is true but does it mean that this practice is based on scientifically incontrovertible evidence? There is a high correlation between a fulminant MH episode and a subsequent positive biopsy in a patient. However, the opposite is not necessarily true. Individuals who are tested on the basis of possible MH susceptibility because of a positive family history are clustered into three patterns of biopsy results: positive, negative, or equivocal. Inevitably, individuals who test positive or equivocal are shielded from MH-triggering anesthetic agents. Therefore, we will probably never know if a positive muscle biopsy

predicts the potential for an MH crisis. The North American Malignant Hyperthermia Registry has been instrumental in looking closely at the presently available biopsy-testing criteria. Most investigators in the field of MH are acutely aware of the many causes of variability of results and realize that the interpretation of biopsy results is fraught with uncertainties. Three years have elapsed since the new standards have been in place, but the key issue of whether a positive biopsy predicts positive clinical risk has yet to be scientifically proven.

Indeed, the strength of our study is that it has allowed us to conclude, independent of biopsy results, that isolated MMS is unlikely to be accompanied by any significant clinical indicators of hypermetabolism. Whether MMS is a variation of MH with mild symptomatology, a graded susceptibility as proposed by Nelson et al. (7), or a benign pharmacologic response to depolarizing agents is not known. Whether an individual anesthesiologist encountering MMS should continue the triggering anesthetic agents or should follow the conservative approach of Drs. Rosenberg and Shutack and desist, depends on one's knowledge of the most likely clinical course of MMS and on one's ability to recognize and to deal with a fulminant MH crisis. Our study reports retrospectively our experience with 57 cases of isolated MMS and points out that by continuing the triggering anesthetic agents, there was no increase in long-term morbidity when compared with the outcome data over the same period for 42,000 pediatric patients who were anesthetized. We do not intend to proselytize others, especially those unfamiliar with the management of MH. However, we do want to provide data that could help anesthesiologists make informed decisions regarding the management of MMS and to question such prevailing dogma based on incomplete scientific evidence. Our paper raises issues that need to be examined in controlled prospective studies.

Leena R. Patel, MD, FRCPC

Department of Anesthesia

Section of Pediatric Anesthesia

Deepak Bose, MD, PhD

Departments of Anesthesia, Pharmacology and Therapeutics, and Internal Medicine

Judith A. Littleford, BSc, MD

Department of Anesthesia

University of Manitoba

Faculty of Medicine

Winnipeg, MB, Canada R3A 1S1

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Triggering Agents Continued After Masseter Spasm: There Is Proof in This Pudding!

To the Editor:

The article by Dr. Littleford et al. underscores important points and corroborates our experiences (1). In 57 children with isolated masseter spasm, general anesthesia was continued with an inhalation agent; yet, the previously predicted hypermetabolism *did not follow*. Thus, the contention "isolated masseter spasm heralds, or is the harbinger of, malignant hyperthermia..." (2,3) can be laid to rest: it does not herald, nor is it a harbinger. This experience is consistent with four reports (4-7).

The hallmark of malignant hyperthermia (MH) is the presence of hypermetabolism, which results in an increased carbon dioxide (CO₂) production (8,9); without an increased CO₂ production, MH has not occurred. Thus, spontaneous ventilation would have indicated hypermetabolism in Dr. Littleford's patients as a considerably increased minute ventilation, which did not occur in any patient. However, the lead time to detection of respiratory signs may be quite variable, as the anesthesiologist intermittently notes respirations; initial changes may escape attention. An increased CO₂ production is reflected in a raised end-tidal level of CO₂ (P_{ET}CO₂); by current methodology, it is the most sensitive and specific sign for the presence of hypermetabolism, and also the earliest (9). Thus, P_{ET}CO₂ measurements during controlled ventilation with constant minute ventilation allows for early detection of an increased CO₂ production and, therefore, for early treatment of "the real thing."

For purposes of intraoperative management, Dr. Littleford et al. make a clear distinction between isolated masseter spasm and masseter spasm associated with rigidity of other muscle groups. "Isolated" pertains to rigidity of the masticatory muscles in the absence of muscle rigidity elsewhere in the body. Isolated specifically does not reflect on other often cited signs such as arrhythmias and hypertension, which have been long associated with the induction of general anesthesia, specific drugs, and tracheal intubation. Post hoc tests (creatine kinase [CK] and myoglobin levels, contracture tests) cannot be used intraoperatively either, while these tests and cardiovascular signs lack any specificity for hypermetabolism. The authors do not appear to rely on the cardiovascular signs or on plasma levels for identification of MH susceptibility; neither do we. Isolation of the rigidity, in the absence of hypermetabolism, was key in their, and is in our, decision to proceed with anesthesia. Generalized rigidity has been more clearly identified with neuromuscular diseases and morbidity causing more uncertainty about continuation of anesthesia.

An elevated serum CK level is consistent with muscle membrane permeability changes and with cell injury for which it is a sensitive indicator. However, an elevated serum CK level lacks specificity, whether it concerns physiology (10,11), pharmacology, or pathology (12); their differentiation requires corroborating evidence. It is not clear why CK is released at times and what its clinical importance

is beyond "a muscle process" (except during extreme myoglobinuria [13]). For example, CK levels of healthy volunteers can be large (up to 11,000 IU/L after one arm exercise for 20 min, 180,000 IU/L after leg exercise for 20 min), delayed (with peaks 3-5 days after exercise, with normal values returning only after 8 or more days), and show great variation (10,11). In view of the variation in CK levels in healthy individuals, I conclude that the banding of subjects on the basis of a CK of 10,000-20,000 (14-17) is too naive to discriminate the potential MH-susceptible individual from those that are not susceptible. This is underscored by Dr. Littleford's study results from 68 subjects with values of 19,000-77,503 (mean) and 138,000-184,200 IU/L (peak). It should be remembered that a raised serum CK level is common, whereas MH is rare. Dantrolene treatment has recently been recommended for isolated masseter spasm and for potential CK or myoglobin increases (16,17). A scientific foundation for such therapy has not been established (13); neither is treatment supported by the experience of Dr. Littleford's 57 patients.

Since 1988, we have observed isolated masseter spasm after succinylcholine "relaxation" in 6 subjects, aged 3-14 yr; all patients were intubated, and halogenated agents were continued for 1-3 h. Minimal P_{ET}CO₂ changes were noted; hypermetabolism could not be demonstrated, and, therefore, dantrolene was not administered. In our institution, four patients with a history of isolated masseter spasm underwent an anesthetic induction with halogenated agents. Two of them received nondepolarizing relaxants, the others received 1.5 mL/kg of succinylcholine intravenously. Masseter spasm did not reoccur in one; in the other, the mandibular incisors indented the endotracheal tube, while jaw motion was tracked continuously with a kinesiograph. Subsequent jaw openings demonstrated an increased stiffness that did not permit the opening to reach baseline until 10 min after succinylcholine administration. Anesthesia lasted at least 60 min, and hypermetabolism could not be demonstrated.

Experience with the halothane-caffeine contracture test would suggest that perhaps 50% of Dr. Littleford's subjects may be labeled "susceptible" to MH (14,18,19). Yet, no subject in this series became hypermetabolic, thereby seriously challenging the value of contracture testing and its ability to distinguish the MH-susceptible from the nonsusceptible human. We are left to wonder what the meaning is of the halothane-caffeine contracture test.

Abraham F. L. van der Spek, MD

Department of Anesthesiology
Med Inn Building C4139 Box 0800
University of Michigan
Ann Arbor, MI 48109-0800

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Pressure Monitoring Hose Causes Leak in Anesthesia Breathing Circuit

To the Editor:

Anesthesia breathing circuit leaks are a common problem (1). We discovered a tear in a pressure monitoring hose adjacent to the metal adapter that connects to the anesthesia machine (Figure 1). The hose damage was probably caused by a stretcher or bed that bumped into the adapter. We recommend that our colleagues consider this hose as a

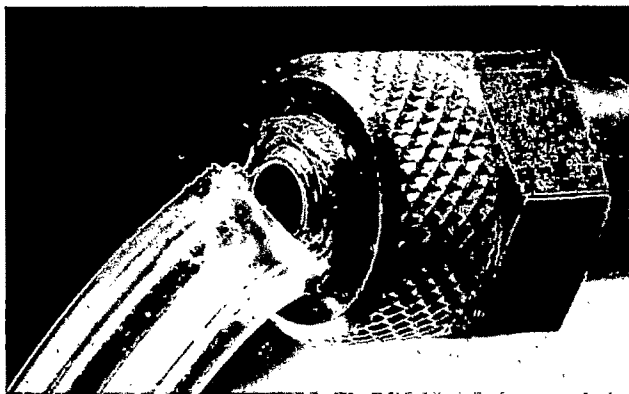


Figure 1. The hole in the plastic pressure monitoring hose is visible where it attaches to the metal adapter.

potential leak source when searching for breathing system leaks.

Oliver Lee, MD
New York University School of Medicine
New York, NY 10016

Richard M. Sommer, MD
Anesthesiology Service, 190
Department of Veterans Affairs Medical Center
423 East 23 Street
New York, NY 10010

Reference

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Analgesic Synergy Between Intrathecal Opioids and Local Anesthetics

To the Editor:

We read with interest the article by Badner et al. (1) that failed to find an enhancement of analgesia and that reported possible increased morbidity when combining low-dose bupivacaine and epidural fentanyl after knee surgery. They clearly demonstrate that postoperative infusion of epidural fentanyl with or without administration of low-dose bupivacaine results in acceptable analgesia as evidenced by visual analogue scale (VAS) scores of 15-40 mm (0 = no pain and 100 = worst pain ever). However, the experimental design may not have permitted a finding of analgesic synergy. That is, in the face of the adequate analgesia produced by epidural administration of fentanyl alone, it would be difficult to show statistically significant differences (i.e., reduction) in VAS scores after the addition of low-dose bupivacaine to the original dose of fentanyl. A more useful approach may have been to determine VAS scores after a 50% reduction of the epidural dose of fentanyl in combination with low-dose bupivacaine.

The conclusion that the addition of low-dose bupivacaine to epidural fentanyl may increase morbidity suggests an interaction. However, it is highly unlikely that morbidity could have been equal or less as the same dose of fentanyl was administered to both groups. The objective when coadministering intraspinal opioids with low-dose local anesthetics should be to (a) reduce the dose of opioid, (b) maintain or enhance the degree of pain relief, and (c) decrease the incidence of adverse effects.

We have recently concluded a study that clearly demonstrates, by quantitative isobolographic analysis, analgesic synergy between intrathecal morphine and lidocaine during both visceral and somatic nociception in the rat. Moreover, the supraadditive antinociception occurs at dosages that do not impair motor function. There is scientific justification and therapeutic rationale for coadministration of intraspinal opioids and local anesthetics in pain management. However, they should be combined in ratios that

maintain or improve analgesia while decreasing adverse effects.

Timothy J. Maves, MD

G. F. Gebhart, PhD

Departments of Anesthesiology and Pharmacology
University of Iowa College of Medicine
Iowa City, IA 52242

Reference

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In Response:

We thank Drs. Maves and Gebhart for their interest in our paper comparing the use of epidural fentanyl with epidural fentanyl and 0.1% bupivacaine (1). Our study was designed only to compare the concentrations used and not to determine if synergy does or does not occur between epidural opioids and local anesthetics. Our conclusions were therefore intended to convey the fact that the addition of 0.1% bupivacaine per se does not improve the efficacy of epidural fentanyl in a concentration of 10 $\mu\text{g/mL}$. We chose these concentrations as they are used routinely and have been reported by others to be superior to this concentration of epidural fentanyl alone (2-4). We cannot argue with Drs. Maves and Gebhart's findings, as well as the findings of others (5), that the addition of local anesthetics to *intrathecal* opioids improves analgesia in rats. Our study simply showed that 0.1% bupivacaine is not the appropriate concentration for *epidural* fentanyl in a 10- $\mu\text{g/mL}$ concentration in patients after total knee joint replacement. Although we suggested that morbidity was increased with the addition of 0.1% bupivacaine, the one case of respiratory depression was most likely due to the epidural fentanyl and not to an additive effect of the combination. In fact, as we suggested in the discussion, a higher concentration of bupivacaine may be necessary to allow a decrease in epidural fentanyl requirements and thereby show a synergistic effect. We are presently investigating this possibility in an ongoing study.

Neal H. Badner, MD, FRCP(C)

Wendy E. Komar, RN

Department of Anaesthesia, University Hospital
University of Western Ontario
London, Ontario, Canada N6A 5A5

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Addition of Low-Dose Bupivacaine to Epidural Fentanyl Infusion

To the Editor:

Badner et al. (1) state that low-dose bupivacaine does not improve epidural fentanyl infusion analgesia after knee surgery. We find this conclusion to be premature.

In their study, the infusion rate was begun at 60 $\mu\text{g/h}$ in both groups, with increases of 20 $\mu\text{g/h}$ with any patient complaint of significant pain. These doses are not unusual for the early postoperative period, but there was no provision for decreasing the dose in patients who did not complain of pain or of weaning those whose doses had been increased. Infusion rates were only decreased if patients became somnolent. This methodology resulted in steadily increasing dosages over the first and second postoperative days, such that by the second day, the average infusion rate in both groups was 80 $\mu\text{g/h}$, an unusually high rate for this late in the postoperative course (2,3). In our practice, hourly dosages progressively decrease from 60-80 μg on the day of surgery to 40-60 μg on the first postoperative day, and 30-40 μg on the second postoperative day. The average serum fentanyl levels in the study increased to 2 ng/mL by the second postoperative day, significantly higher than that found in other studies (3,4), producing unacceptably high incidences of side effects (4,5). When both groups are given such high doses of fentanyl, it may be difficult to tell whether addition of bupivacaine makes any difference.

If the clinical goal of adding bupivacaine is to decrease the dose of fentanyl, why not set up the study to routinely decrease the infusion rate on patients who are comfortable (3)? One could also use patient-controlled analgesic or similar techniques, as our group and many others do, to optimize fentanyl dosage (4,6,7). Either of these methods would allow a possible fentanyl-sparing effect of bupivacaine to be more easily determined.

Adding low-dose bupivacaine to epidural fentanyl infusions may be beneficial in certain patient populations. More study is needed before conclusions are drawn.

Wilfred Prados, MD

Department of Anesthesiology
University of Alabama at Birmingham
619 South 19th Street
Jefferson Towers, Suite 845
Birmingham, AL 35233

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In Response:

We thank Dr. Prados for his interest in our paper comparing the use of epidural fentanyl with epidural fentanyl and 0.1% bupivacaine (1). Our method of infusion rate adjustment was designed to allow titration to patient requirements, and as noted, specifically included criteria for decreasing the rate. The fact that the rate needed to be increased indicates that our patients were experiencing more pain, possibly because of increasing mobilization that is routine on the first and second postoperative days. Dr. Prados claims that the epidural requirements should be decreasing at this time; however, of the two papers that he refers to, the study by Bodily et al. (2) only dealt with the first 24 h, during which time the patients' epidural fentanyl requirements only decreased in the first 2 h. In the second study, that by Guillen et al. (3), the protocol was to begin decreasing the epidural infusion rate on the third postoperative day and not sooner. In fact, the amounts of epidural fentanyl that our patients required and the resulting serum concentrations that occurred are consistent with those from a variety of other patient populations (4-6).

Whether the use of patient-controlled epidural fentanyl analgesia decreases epidural narcotic requirements was not addressed by Bodily et al. (2) or Chrubasik et al. (7) and needs further verification other than the 13 patients reported as an abstract by Boudreault and Brasseur (8).

Neal H. Badner, MD, FRCP(C)
Wendy E. Komar, RN
Department of Anaesthesia, University Hospital
University of Western Ontario
London, Ontario, Canada N6A 5A5

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Catheter Spinal Anesthesia and Cauda Equina Syndrome: An Alternative View

To the Editor:

As proponents of continuous spinal anesthesia (CSA), we were distressed by the reports of cauda equina syndrome presented by Rigler et al. (1). We find our experience with more than 200 continuous spinal anesthetics differs markedly from the authors', and we take issue with several points as they were presented.

First, careful perusal of the affected patients reveals that two of the four patients had preexisting neurologic abnormalities. Patient 1 had experienced continued pain after lumbar laminectomy and cannot be considered to have "normal" function. Patient 3 had received lumbar parasympathetic blocks for presumed reflex sympathetic dystrophy. One must consider the possibility that these patients were already neurologically compromised, and intraoperative events tipped the scales toward a permanent cauda equina syndrome. In addition, one must question the wisdom of selecting a regional anesthetic technique for a patient with preexisting neurologic deficits.

We strongly disagree with the statement that "clear guidelines for the safe administration of local anesthetics . . . with CSA remain to be established." Nearly a century of clinical practice and careful scientific study has produced a body of both evidence (2,3) and opinion (4) that defines a clear therapeutic window for the safe administration of local anesthetics in the subarachnoid space. This body of knowledge, elegantly discussed by Rigler et al., has improved the safety of spinal anesthesia. Hence, it is difficult to justify a clinical practice that requires amounts of local anesthetics that are far in excess of standard "single-shot" doses to achieve adequate neuroaxial blockade. The use of large amounts of lidocaine "tailored to achieve appropriate dermatomal level" or the use of 28 mg of tetracaine (some "old" and some "new") to achieve initial subarachnoid block appears to disregard the narrow toxic-to-therapeutic ratio of local anesthetics.

The authors point out that Lemmon and Paschal (5) discussed "individual tolerance" and advocated using large doses of local anesthetics to overcome this phenomena. We have also reviewed this literature and have developed a different (and we believe safer) approach to this phenomena of "relative resistance." Dripps (6) noted that changing local anesthetic agents frequently overcame an incomplete block and increased the success rate of spinal anesthetics. Our current practice advocates the use of alternative local anesthetic agents and/or narcotics if the initial agent does not have the desired effect. This practice has led to our low agent-related failure rate (defined as failed CSA after technically correct subarachnoid catheter placement). Although the pioneering work of Lemmon, Dripps, Tuohy (7), and Apgar (8) has much to offer the practitioner of CSA, their work must be evaluated in its proper historical context. Much has changed in the 50 yr since their work was first published. We do not currently use malleable spinal needles in preference to 3.5F ureteral

catheters, nor should we adhere to techniques espoused in the absence of technologically improved equipment, agents, and advanced understanding of local anesthetic action and toxicity.

The issue of local anesthetic maldistribution through microcatheters may indeed be a problem (9); however, 25% of the cases reported by Rigler et al. occurred with a macrocatheter technique. In this light, the implication of microcatheters as the cause of neurologic catastrophe appears less than solid. The question of "tachyphylaxis" has yet to be defined. Our experience with more than 50 cases of postoperative intrathecal local anesthetic infusions has failed to show any evidence of either tachyphylaxis or neurologic injury despite infusion durations of several days (10).

Our practice (and recommendations) differ from those of Rigler et al. For CSA we use initial doses of local anesthetics that have been found to be safe from many years of clinical practice; i.e., 25–100 mg of 5% lidocaine, 5–15 mg of 0.5% or 0.75% bupivacaine, or 5–10 mg of 1% tetracaine. If the initial block is successful, then the concentration and baricity of subsequent doses is tailored to produce surgical anesthesia in the desired field. We believe there is no need to continue producing sacral anesthesia with hyperbaric solutions when the surgical field does not involve this region. When judicious initial doses of local anesthetic fail to produce adequate anesthesia, we recommend using different local anesthetic agents, narcotics (fentanyl, sufentanil, or meperidine), or combinations thereof to achieve adequate blockade. We have found this practice to be both effective and safe. Our incidence of failure with CSA has been reduced to only those instances in which technical difficulties with catheter placement occur.

In conclusion, we applaud the courage of Rigler et al. in presenting cases that were managed in an atypical fashion, but we strongly disagree with their conclusions. The authors may have defined the numerator of a potential problem, but the denominator remains to be determined. We feel from our experience that the incidence of cauda equina syndrome (or other neurologic injuries) with catheter spinal anesthesia is not a common occurrence. We believe that rather than slavish adherence to arbitrary guidelines, prudent practitioners of CSA should thoroughly acquaint themselves with both the contemporary and historical literature regarding CSA and arrive at their own conclusions. Practitioners may then find that the fault lies not with their catheter but rather with themselves.

Brian K. Bevacqua, MD
William F. Cleary, MD
Alexey V. Slucky, MD
Department of Anesthesiology
Case Western Reserve University
Cleveland, OH 44106

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To the Editor:

We read the extremely interesting article by Rigler et al. concerning cauda equina syndrome after CSA (1). The article certainly does present four cases of cauda equina syndrome after the use of CSA. However, the complications that ensued are more accurately attributed to local anesthetic toxicity, probably an overdose combined with possible over-concentration (not "maldistribution") rather than the technique of CSA itself. In fact, the authors make the case for this in their explanation. However, in all four cases high initial doses of local anesthetic were administered. Why did the authors choose such large doses in conjunction with continuous spinal technique? The ability to administer additional incremental doses of local anesthetic, such as during the continuous catheter technique, allows the anesthesiologist to start the technique with lower doses when compared with single-shot spinal anesthesia.

The question of maldistribution is also raised by the authors. We believe the problem may be better explained as a result of injecting high concentrations of local anesthetic into a small area. If such high doses are injected through a 28-gauge catheter, and this will be a slow injection, this may bathe exposed unmyelinated neural tissue in high concentrations. Therefore, we believe the title should reflect the high doses used and the small-lumen catheter employed in three of the four cases. Both are more significant contributing factors than the continuous technique itself.

Alan L. Rosenberg, MD
Martin I. Gold, MD
Anesthesiology Service (139)
University of Miami School of Medicine
VA Medical Center
1201 NW 16th Street
Miami, FL 33125

Reference

1. Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg* 1991;72:275–81.

To the Editor:

Dr. Rigler and his colleagues (1) are to be congratulated on publishing (as a guide and warning to others) their cases of cauda equina syndrome after CSA and also on their wide-ranging consideration of the possible etiologic factors. However, I would like to raise two factors that are mentioned in their paper but which I believe require more emphasis.

First, each patient received a solution that had a tonicity (~450–500 mOsm) that was significantly in excess of body fluid. Those portions of the spinal nerve roots that lie in the

subarachnoid space do not have nerve sheaths and are, I would suggest, very susceptible to osmotic damage. When hypertonic solutions are injected during single-shot spinal anesthesia, they disperse widely and are rapidly diluted. However, injection through a catheter can occasionally lead to restricted spread and so the cauda equina may be exposed to relatively undiluted solution.

The second point relates to the usual reaction to such restricted spread, which is to give a further dose in the hope of extending the block, even though there is now good evidence that extent of block is only weakly related to the amount of solution injected (2). When more solution is injected it will not necessarily result in extension of the block, but simply cause a further localized increase in tonicity and in the risk of nerve damage.

I totally agree that only small increments of drug should be given through a spinal catheter and that the response to a very restricted block should not be a simple repeat injection but a careful consideration of the causes, particularly the possibility that too much catheter has been inserted. I would also suggest that only solutions with a tonicity near to that of cerebrospinal fluid be used. The solution beginning to be favored here for CSA is 0.5% bupivacaine in 0.8% dextrose (3), which is produced by mixing thoroughly 9 mL of plain 0.5% bupivacaine with 1 mL of the United Kingdom commercial preparation of "heavy" 0.5% bupivacaine. The mixture is injected in 0.5-1-mL increments.

J. A. W. Wildsmith, MD, FCAnaes
Department of Anaesthesia
The Royal Infirmary
Edinburgh, EH3 9YW, United Kingdom

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In Response:

We appreciate the interest and concern expressed in these three letters. Our manuscript described four cases of cauda equina syndrome after CSA. Our purpose was to alert clinicians to this potential risk, to suggest a possible cause, and to use the available data to begin to establish much-needed guidelines for the safe administration of local anesthetic through an indwelling subarachnoid catheter.

Dr. Bevacqua et al. disagree with our assertion that clear guidelines have yet to be established for the safe conduct of CSA. They cite two references as the "body of evidence" defining a clear "therapeutic window" for the safe administration of local anesthetic in the subarachnoid space. The first is a study of intrathecal injections in rabbits that was performed "to study the relationship between anesthetic concentration [not dose] and impaired neurological function" in which the authors conclude that "none of the local anesthetics studied produced persistent neurologic damage in concentrations used clinically" (1). Their second reference (a review article) devotes less than one paragraph to the question of local anesthetic neurotoxicity and includes

the comment "Concerns regarding spinal cord damage resulting from mechanical trauma or spinal cord irritation from local anesthetic solutions are not well founded" (2). Although there are both experimental and human data (reviewed in our manuscript) to suggest that currently used local anesthetics can result in neurotoxic injury, the "therapeutic window" has never been clearly defined. Bevacqua et al. also cite as "opinion" a 1961 review article by Nicholas Greene that contains insightful comments regarding the advisability of limiting concentration and dose of local anesthetic but does not provide clearly defined guidelines for the safe practice of CSA (3).

The guidelines offered in our manuscript are not arbitrary, but derived from analysis of the four cases and a review of existing clinical and experimental data. We do not advocate "slavish adherence" to any set of guidelines, but assume clinicians will recognize the importance of understanding the information upon which guidelines are based and will appreciate that guidelines require modification as additional information becomes available.

Dr. Bevacqua et al. appear to confuse our recommended guidelines with the cases from which they were derived. We have suggested the lowest effective concentration of local anesthetic be used for CSA. This recommendation is based on data indicating that the risk of neurologic injury is, at least in part, concentration-dependent. If maldistribution occurs, the concentration of local anesthetic will not be adequately diluted by cerebrospinal fluid. We believe that their suggestion to use 5% lidocaine, 1% tetracaine, and 0.75% bupivacaine is unwise; these concentrations are in excess of what is needed for adequate blockade.

They also recommend administering an alternate local anesthetic if anesthesia is inadequate after as much as 100 mg of 5% lidocaine, but provide no data to demonstrate the increased safety of administering a second agent rather than additional doses of the same local anesthetic. They base their practice of changing local anesthetics on a study by Dripps (comparing CSA performed with a malleable spinal needle or with a 3.5F ureteral catheter) in which administration of a second agent produced satisfactory anesthesia in seven cases after failure of an "acceptable" dose of the first local anesthetic (4). Dripps even questioned the significance of this observation, commenting that "[resistance] may be a cause for failure, although seven such patients in a group of 486 seem excessive. The possibility must be considered that in some instances the initial solution contained only the solvent (glucose or cerebrospinal fluid)." If maldistribution of anesthetic is suspected, we have suggested using maneuvers such as changing patient position, altering the lumbosacral curvature, switching to a different baricity of local anesthetic, and/or manipulating catheter position to provide adequate extension of the block. If these maneuvers fail, administration of a second local anesthetic likely will distribute in the same restricted pattern, adding to the potential for neurotoxicity. It appears far safer to abandon CSA if such maneuvers do not provide well-distributed anesthesia.

We are concerned about Dr. Bevacqua et al.'s suggestion to use intrathecal local anesthetic solutions to provide postoperative analgesia of several days' duration. There are animal data demonstrating that long-term infusions confer

substantial neurotoxic risk, e.g., significant neurologic deficits have been observed in rats given subarachnoid infusions of 1.5% lidocaine for 36 h but not in rats given the same infusions for only 3 h (5).

Dr. Bevacqua et al. suggest that their experience with CSA differs markedly from ours. This comparison is inappropriate because our manuscript does not describe an overall experience with CSA. Although we described four cases of cauda equina syndrome after CSA, we were aware of several thousand cases of CSA performed at multiple institutions. No doubt, a significant reporting bias exists in the collection of these four cases (we have not defined the "numerator" of this problem). Nevertheless, a reasonable estimate is that the incidence of this complication is no greater than 1 per 1000 cases of CSA. On the surface, Dr. Bevacqua et al.'s experience might appear to differ because they have not observed a single neurologic complication in an unpublished series of 200 cases of CSA. However, if the 1 per 1000 estimate is correct, there is an 82% chance of not encountering a case of cauda equina syndrome in 200 cases (6), suggesting that their "true" long-term incidence of cauda equina syndrome may actually be no different from "ours".

They question whether two of the patients were neurologically compromised preoperatively and whether "intraoperative events tipped the scales toward a permanent cauda equina syndrome." However, the two patients in question had no apparent preoperative neurologic deficit, but rather chronic pain. Moreover, the preoperative symptoms were not consistent with the observed postoperative sacral neurologic deficits, making an additive effect highly unlikely; and the lesions observed postoperatively in these patients were similar to those observed in the two patients without preexisting abnormalities. Dr. Bevacqua et al. further suggest that the choice of spinal anesthesia was ill-advised in the two "neurologically compromised" cases, but offer no data to support this contention. Most current anesthesia texts conclude that avoiding spinal anesthesia for patients who have back pain or have undergone lumbar laminectomy is based primarily on "emotional and probably misguided medical legal influences" (7).

We have not implicated microcatheters as the "etiology of neurologic catastrophe." Our postulate is that neurotoxic injury resulted from the combination of maldistribution and a relatively high dose of local anesthetic. Although we have speculated that maldistribution may occur more often with small catheters, it can occur with any catheter size. Three of our cases involved a 28-gauge catheter and one a 20-gauge catheter, and we cited literature indicating that maldistribution has occurred with catheters as large as 3.5F (8).

Finally, we do not view reporting cases of adverse outcome as an act of courage. Reports of adverse outcomes enable others to avoid them. It is essential that we learn and advance, not individually, but rather from our collective experience.

Drs. Rosenberg and Gold have misinterpreted maldistribution to mean something other than restricted distribution resulting in unintentional high concentration of anesthetic in the subarachnoid space. We do not agree that the initial doses of local anesthetic (35-50 mg of lidocaine or 10 mg of tetracaine) were high. However, a major point in our manuscript was that maldistribution combined with

relatively high cumulative doses may result in neurotoxic injury. We do not agree that the title should reflect the use of a small-lumen catheter: that three of the four cases involved a small catheter may only reflect a reporting bias.

Dr. Wildsmith's letter highlights two factors that indeed deserve greater consideration. First, he has suggested greater emphasis on the possible role of hypertonicity in the cause of the observed neural deficits. We agree that hypertonicity may be an important factor potentiating local anesthetic neurotoxicity, though existing data suggest that hypertonicity, by itself, is unlikely to have been the causal factor in these four cases (9,10).

Second, although the role of dose and volume in the spread of anesthesia is somewhat controversial (11), we agree with his emphasis on the importance of considering possible causes of restricted distribution before administering additional doses of anesthetic. If the initial dose has not produced well-distributed sensory anesthesia, additional doses should not be administered without the use of maneuvers to increase the spread of local anesthetic.

Kenneth Drasner, MD

Mark L. Rigler, MD

Department of Anesthesia

University of California, San Francisco

San Francisco, CA 94143-0648

Tom C. Krejcie, MD

Sharon J. Yelich, MD

Department of Anesthesia

Northwestern University

Chicago, IL 60611

Faith T. Scholnick, DO

Department of Anesthesia

Suburban General Hospital

Norristown, PA 19401

James DeFontes, MD

David Bohner, CRNA

Department of Anesthesia

Kaiser Permanente

Orange County, CA 92807

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Book Reviews

Anesthesia for Plastic and Reconstructive Surgery

A. R. Abadir and S. G. Humayun, eds. Chicago: Mosby Year Book, 1991, 467 pp, \$70.00.

This book consists of 20 chapters written by anesthesiologists familiar with plastic and reconstructive surgery and covers everything from anesthesia equipment and monitoring to ophthalmic reconstructive surgery.

Who is this book written for? Some chapters present unnecessary, superficial information suggesting that perhaps the book was intended for surgeons or others interested in a casual explanation of anesthesia for plastic and reconstructive surgery. Examples include: (a) the advice "Auscultation of the chest will reveal whether the endotracheal tube is in the correct position." is incomplete and outdated in the age of capnography; (b) the chapter on anesthesia equipment quotes the American National Standards Institute's requirements published in 1979 instead of the improved standards of the American Society of Testing and Materials; and (c) the technique described for cannulation of the right internal jugular vein provides no measures to differentiate arterial versus venous puncture.

This book contains other, more disturbing deficiencies. It states "evaluation of bleeding profile (PT/PTT) is necessary when patients are taking aspirin regularly"; the appropriate test would be a bleeding time. The chapter on anesthesia monitoring reprints the minimal monitoring standards practiced by Harvard Medical School in 1986, which were a milestone in patient safety at the time. However, further advances have been made. Considering that plastic surgery is frequently performed under heavy intravenous sedation in a nonhospital surgicenter or office setting, the latest standards approved by the American Society of Anesthesiologists in 1989 and 1990 should have been the cornerstone of the monitoring chapter. These newer standards are mentioned in another chapter on cosmetic surgery.

Other chapters are of textbook caliber for practicing anesthesiologists and residents. The chapters on maxillofacial trauma and craniofacial surgery are brief, easily read, well-illustrated discussions of complicated areas. Far more complete and accurate information on anesthesia equipment, monitoring, various anesthetic techniques, and regional blocks can be found in a variety of standard anesthesia textbooks. This book is a convenient collection of information on anesthetic concerns for plastic and reconstructive surgery if the reader understands that the book is superficial, incomplete, and somewhat outdated.

Cornelius J. O'Connor, Jr., MD
Lahey Clinic Medical Center
Burlington, Massachusetts

Anesthesia and Musculoskeletal Disorders Problems in Anesthesia, Volume 5, No. 1

Anne C. P. Lui and Edward T. Crosby, eds. Hagerstown, Md.: J.B. Lippincott, 1991, 177 pp; \$30.00.

Anesthesia for musculoskeletal disorders is described in this very fine monograph produced by the anesthesiologists and two surgeons at the Universities of Ottawa and Toronto. What makes the volume of such merit is that it brings together a multitude of information from many diverse sources, and it is written by experts in their fields. Many chapters describe large clinical series of patients that the authors have personally anesthetized. Airway, respiratory, cardiac, and neurologic management of these patients are described in great detail.

One of the major problems encountered with rheumatoid arthritis, ankylosing spondylitis, scoliosis, and other musculoskeletal disorders relates to tracheal intubation. The first chapter has an excellent discussion on the cervical spine. However, the same authors in the next chapter on trauma and the adult cervical spine shy away from clear guidance for airway management of the patient with multiple-system trauma and spinal shock.

The chapters on anesthetic concerns for scoliosis surgery and cardiovascular manifestations of musculoskeletal disease are especially noteworthy, comprehensive, and authoritative. The descriptions of a wake-up test and sensory evoked potential monitoring in the chapter on scoliosis are excellent. The cardiovascular aspects of common and rare musculoskeletal disorders are precisely summarized in two tables in this chapter and then discussed in the context of their involvement with the pericardium, myocardium, valves, conducting system, and vasculature. Useful additional chapters summarize the muscular dystrophies, myasthenia gravis, malignant hyperthermia, and musculoskeletal disorders in pregnancy.

The weaknesses of the volume are that there is some repetition and contradiction. Rheumatoid arthritis, ankylosing spondylitis, and Duchenne's muscular dystrophy are discussed in several different sections as is hypotensive anesthesia. Various authors recommended several different techniques and levels of hypotension for reducing blood loss, but the important and controversial topic of hypotensive anesthesia for spinal surgery is not comprehensively discussed. The chapter on respiratory pathophysiology in musculoskeletal disorders is at odds with the general thrust of the rest of the volume in that it merely presents basic respiratory physiology. What this chapter added to our knowledge of specific disorders could have been summarized in a few sentences in the relevant chapters.

The general impression, despite these limited drawbacks, is that this volume is a goldmine of useful information written by experts in their fields. Nowhere else is so much authoritative information available on anesthesia and

musculoskeletal disorders. I would heartily recommend purchase by faculty and practitioners whose interests lie in orthopedic and neurosurgical anesthesia. Residents should have access to this volume in every departmental library.

Colin F. Mackenzie, MD
University of Maryland
School of Medicine
Baltimore, Maryland

Introduction to Dental Local Anesthesia

Hans Evers and Glenn Haegerstam, eds. Switzerland: Mediglobe SA, 1990, 96 pp, \$39.00.

Neural blockade is an essential component of the daily practice of dentistry. Evers, a dentist, and Haegerstam, a physician, have written an excellent introductory text on the use of neural blockade in dentistry. The beautiful artwork of Poul Buckhoj and the clear color photographs have been skillfully integrated to yield a superb "how-to-do-it" handbook of regional anesthesia of the mouth and face.

The book is divided into five sections. The first section provides a concise overview of the anatomy of the trigeminal nerve and its branches. Also included in this section is a review of the physiology of the peripheral nerve and the pharmacology of local anesthetics as they apply to clinical practice.

Section 2 presents considerations that are important to the anesthetist performing nerve blocks, including the emotional preparation of the patient, patient comfort, patient positioning, and the use of preinjection topical anesthesia. Clinical issues including local anesthetic onset time and spread, as well as practical suggestions on how to decrease the pain of injection, are discussed.

Anesthesia of the upper jaw and anesthesia of the lower jaw are the subjects of sections 3 and 4, respectively. A review of the clinically relevant anatomy for each nerve block technique is clearly presented utilizing a combination of drawing, photograph, and text. Practical suggestions to improve the efficacy of each technique are given, along with a drawing clearly delineating the extent of anesthesia that should be expected if the anesthetic technique is properly performed.

Section 5 presents the reader with some of the reasons why a nerve block may fail. Patient variation, improper needle placement, infection, and intravascular injection are discussed. Also presented is a brief review of the potential complications encountered when performing neural block-

ade of the face and mouth. In view of the fact that 2,000,000 dental nerve blocks are performed daily, these complications are exceedingly rare.

Although intended for the dental student and practicing dentist, the information presented in this text would be of use to the anesthesiologist involved in the care of patients with headache and facial pain. The techniques presented also have clinical utility for the anesthesiologist involved in the care of the adult and pediatric patient undergoing facial or oral surgery.

Steven D. Waldman, MD
Pain Consortium of Greater Kansas City
Leawood, Kansas

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Carlisle JR, Sanbar SS, Rheinstei PH, Seifert JB, eds. *Legal Medicine, Legal Dynamics of Medical Encounters*. 2nd ed., St. Louis: Mosby Year Book, 1991, 670 pp.

Dantzker DR, ed. *Cardiopulmonary Critical Care*. 2nd ed. Philadelphia: W.B. Saunders, 1991, 851 pp, \$99.00.

Gardner AM, Haynes A, Winter RR, DeKornfeld TJ. *Anesthesiology Specialty Board Review*. 8th ed. New York: Medical Examination Publishing Co., 1991, 255 pp, \$37.00.

Taswell HF, Pineda AA, eds. *Autologous Transfusion and Hemotherapy*. St. Louis: Blackwell Scientific Publications, 282 pp, \$54.95.

Erratum

Book Review. Vol. 73, No. 1, July 1991, p. 100.

The title of the book should be *Chronic Pain* (not *Problems in Anesthesia*), edited by B.D. Hare and P.G. Fine. The book is Volume 4, No. 4 (December 1990) of the Problems in Anesthesia Series published by JB Lippincott, Philadelphia, Pa.

The reviewer of the book is Gabor (not Gabur) B. Racz, MD.

Treatment of Acute Systemic Toxicity After the Rapid Intravenous Injection of Ropivacaine and Bupivacaine in the Conscious Dog

Hal S. Feldman, DSc, G. Richard Arthur, PhD, Mikko Pitkanen, MD, PhD,
Ronald Hurley, MD, Ann Marie Doucette, BA, and Benjamin G. Covino, MD, PhD

Department of Anesthesia Research Laboratories, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

Two groups of six beagle dogs received rapid intravenous (IV) injections of ropivacaine or bupivacaine on two occasions in a blinded random fashion. Initially, a dose sufficient to cause convulsions (CD) was given followed by twice the CD ($2 \times \text{CD}$), which was administered 48 h later. The CD of bupivacaine (4.3 mg/kg) and ropivacaine (4.9 mg/kg) caused significant ($P < 0.05$) increases in heart rate and mean arterial blood pressure. There was no difference between drug groups. Seizures were abolished by 10 mg/kg of intravenous thiamylal. Endotracheal intubation and controlled respiration with O_2 -enriched air with no other treatment resulted in rapid and complete recovery in all dogs. All dogs receiving $2 \times \text{CD}$ of bupivacaine (8.6 mg/kg) or ropivacaine (9.8 mg/kg) were initially treated with thiamylal and mechanical ventilation. Two dogs in the bupivacaine group developed hypotension, respiratory arrest, ventricular tachycardia, and ventricular fibrillation, which were resistant to closed chest cardiac massage, treatment with epinephrine, bretylium, and atropine,

and direct current cardioversion. The four remaining dogs in the infusion group were successfully resuscitated. All of the animals in the ropivacaine-treated group survived the administration of the $2 \times \text{CD}$ dose. Mild hypotension developed in one dog and was treated with intravenous epinephrine (0.75 mg). This resulted in nodal tachycardia, which was abolished after treatment with bretylium. Another dog had two 1-s bursts of premature ventricular contractions requiring no treatment. The rapid treatment of convulsions and cardiovascular toxicity resulted in a decreased number of deaths in both groups when compared with dogs from a previously published study in which no therapy was instituted. Thus, early aggressive treatment of central nervous system and cardiovascular system toxicity is capable of reducing the incidence of mortality associated with the rapid intravenous administration of excessive doses of local anesthetics.

(Anesth Analg 1991;73:373-84)

In laboratory animal and human studies, ropivacaine possesses a local anesthetic profile that is similar to that of bupivacaine (1-5). The intravenous dose necessary to produce overt seizure activity in the dog is also very similar to that of bupivacaine (6). However, ropivacaine is less arrhythmogenic and produces less depressant effects on various cardiac electrophysiologic and mechanical variables than does bupivacaine (6-8).

It is possible to resuscitate most animals rendered cardiotoxic by the intravenous administration of large

doses of bupivacaine and lidocaine (9-12). However, no information is available covering the ability to reverse the systemic toxic effects associated with the intravenous administration of excessive doses of the new local anesthetic ropivacaine. This study was designed to mimic the possible clinical situation of an accidental rapid intravenous injection of a large dose of local anesthetic. A regimen of treatment was designed to control seizure activity, provide a patent airway, support respiration and arterial blood pressure, and control or abolish ventricular arrhythmias. Convulsant (CD) and supraconvulsant ($2 \times \text{CD}$) doses of bupivacaine and ropivacaine were administered as rapid intravenous bolus injections in two groups of six conscious dogs in a blinded random fashion. Systemic toxicity was then treated according to a predefined regimen.

This work was supported in part by a grant from Astra Pain Control, Sodertälje, Sweden.

Accepted for publication June 5, 1991.

Address correspondence to Dr. Feldman, BWH Anesthesia Research Laboratory, Massachusetts Biotechnology Park, One Innovation Drive, Worcester, MA 01605.

Methods

Approval for this study was obtained from the Animal Research Committee of the testing facility. Twelve male colony-bred beagle dogs having a mean weight (\pm SEM) of 12.6 ± 0.5 kg and a mean age of 21.0 ± 2.1 mo were used. Dogs were randomly assigned to a drug treatment group ($n = 6$ per group).

Animals were anesthetized with 20 mg/kg of intravenous thiamylal. The left and right sides of the chest and the sternal area were shaved to facilitate direct current cardioversion during the experiment if necessary. Under aseptic conditions polyethylene catheters were introduced into the abdominal aorta and inferior vena cava via the femoral vessels. The catheters were exteriorized at the hock and protected by gauze sponges and tape. These catheters were used for blood pressure recordings and blood sampling. A shortened pulmonary artery catheter introducer was inserted into the right external jugular vein to facilitate the placing of a bipolar electrocardiographic recording catheter in close proximity to the heart. Animals were treated with intramuscular antibiotic (600,000 U of Bicillin C-R Wyeth-Ayerst Laboratories, Philadelphia, Pa.) and allowed to recover for 48 h.

On the morning of the experiment, dogs were secured in the standing position in a canvas sling. The femoral catheters were connected to the appropriate precalibrated transducers for direct recording of blood pressure. The cephalic veins were catheterized utilizing a Quik-Cath (Travenol Laboratories, Deerfield, Ill.) intravenous catheter that was passed percutaneously.

A plethysmograph was secured around the dog's chest and connected to a Grass PT5A volumetric pressure transducer. The transducer was interfaced with a Grass model 7 polygraph to record respiratory rate.

A lead II electrocardiogram (ECG) was recorded using subdermal needle electrodes. An internal ECG was recorded by utilizing a bipolar recording electrode catheter inserted via the implanted introducer in the external jugular vein. The electrode was advanced while the ECG was observed on the polygraph strip chart recorder until the optimal ECG configuration was obtained.

Pre-drug control records consisted of recordings of respiratory rate, heart rate, and arterial blood pressure taken at 30, 20, 10, and 0.5 min before drug administration. After the administration of drug, cardiovascular measurements and data recordings were made at 10-15-min intervals.

Arterial and venous blood samples were taken at regular intervals before and after drug administration. Venous blood (1 mL) was collected and assayed for lactate concentration by a spectrophotometric

technique using the Sigma Diagnostics lactic acid kit. Coefficients of variation for this assay were 5% at 2.66 mmol/L to 4% at 6.66 mmol/L. Samples were stored at 4°C until required for assay. Three milliliters of arterial blood was collected in plain glass tubes that were previously treated with antioxidant [50 μ L of 1 mM reduced glutathione and 1 mM ethylene glycol bis-(β -aminoethyl ether), *N,N,N',N'*-tetraacetic acid solution] for catecholamine determinations. Samples were kept on ice until centrifuged to obtain serum, which was stored at -80°C until required for analysis. Catecholamine analysis was performed using a high-performance liquid chromatography technique with electrochemical detection, adapted from a previously described method (13). Coefficients of variation for this assay were as follows: norepinephrine, 8% at 200 pg/mL to 6% at 6000 pg/mL; epinephrine, 5% at 200 pg/mL to 5% at 6000 pg/mL. Two milliliters of arterial blood was collected in heparinized glass tubes for determination of local anesthetic concentrations. These samples were stored at -20°C until required for gas chromatographic analysis utilizing a modification of a previously described technique (14). Coefficients of variation for this assay were as follows: ropivacaine, 8% at 0.1 μ g/mL to 5% at 1.0 μ g/mL; bupivacaine, 8% at 0.1 μ g/mL to 3% at 1.0 μ g/mL. Local anesthetic concentrations are reported as micrograms of drug hydrochloride per milliliter of whole blood. An additional 1 mL of arterial blood was collected in heparinized syringes for immediate analysis of pH, arterial O₂ tension (Pao₂), and arterial CO₂ tension (Paco₂) utilizing a Corning model 168 blood gas analyzer.

After the 30-min control period, solutions of local anesthetic were administered manually as an intravenous bolus injection via a forelimb vein catheter over 30-60 s. The volume of injectate was kept constant (CD at 10.0 mL and $2 \times$ CD at 20.0 mL) by the addition of sterile saline for injection. Each injection was followed immediately by a 2.0- to 3.0-mL flush of saline solution.

The CDs of bupivacaine (4.3 mg/kg) and ropivacaine (4.9 mg/kg) were based on the results of a previous study (6). The CD was administered on the first experimental day and two times the CD was given (48 h later) on the second experimental day.

The resuscitative procedures that were followed after the administration of local anesthetic were dictated by the signs and symptoms of systemic toxicity. Treatment was directed at the following: control of seizure activity, support of ventilation, treatment of arrhythmias, and support of circulation. The order of treatment varied depending on what type of toxicity was seen. The most life-threatening toxicity was dealt with first. Procedures for various toxic reactions were as follows:

1. Seizures were treated with 10 mg/kg of intravenous thiamylal after 30 s of convulsive activity followed by intubation and ventilation with oxygen-enriched room air.
2. Hypotension was defined as a mean arterial blood pressure of 50 mm Hg or less persisting for 15 consecutive seconds. Treatment consisted of intravenous epinephrine (0.75 mg), which was repeated several times if necessary. If this was not effective to control hypotension and bradycardia, atropine (0.8 mg) was given.
3. Ventricular tachycardia, bursts of ventricular tachycardia, or frequent premature ventricular contractions (premature ventricular contractions with a rate greater than 5/min) were treated with intravenous bretylium (20 mg/kg) administered over 1 min.
4. Ventricular fibrillation was treated with external cardiac massage and direct current cardioversion was then attempted using external transthoracic paddles. External chest compressions were continued between cardioversion attempts.

Statistical analysis consisted of analysis of variance and Student's *t*-test for paired data (when comparing changes from predrug control across time within a drug/dose group) and Tukey HSD multiple-comparison test and unpaired Student's *t*-test (for comparison between drug groups). Frequency of occurrence data were analyzed using the Fisher's exact test. Values of $P \leq 0.05$ were considered significant.

Data presented are mean \pm SEM, $n = 6$ unless otherwise noted. Predrug control data consists of four values (30, 20, 10, and 0.5 min), which were pooled for each of the six dogs in a drug group. Thus, the control mean values for a treatment group are based on an n of 24.

Results

The Convulsant Dose

There were no significant differences between treatment groups in any of the measurements made during the predrug control period.

The intravenous administration of 4.3 mg/kg of bupivacaine and 4.9 mg/kg of ropivacaine resulted in overt seizure activity in all animals. Thiamylal terminated convulsions in all animals. Immediately after termination of convulsions, tracheal intubation and controlled ventilation with oxygen-enriched room air was instituted. All animals in both groups survived without requirements for cardiovascular support. There was no significant difference between drug groups in the time to the start of seizures, the time of thiamylal

administration, the time of cessation of seizures, and the time of intubation or extubation.

Within 30 s of administration of the convulsive dose and in conjunction with overt seizure activity, a 54% increase in heart rate occurred in both groups ($P < 0.01$) (Tables 1 and 2). After the abolition of seizures, heart rates in both groups decreased to predrug values and remained there for the duration of the experiment.

The CD of either drug caused no significant changes in the PR or QT interval on the ECG. The QRS interval was increased approximately 30% in both treatment groups during the 1-3 min after local anesthetic administration (Tables 1 and 2).

There were rare occasions of atrial premature contractions seen in some animals in both treatment groups during the predrug control period. No other supraventricular arrhythmias were noted. No ventricular arrhythmias were seen in either the bupivacaine or ropivacaine treatment groups after administration of the CD.

Significant increases in systolic, diastolic, and mean arterial pressure occurred in both groups for the 1-min period after drug injection and in conjunction with seizure activity (Tables 1 and 2). Mean arterial blood pressure in the ropivacaine group (180 ± 12 mm Hg) was significantly higher than that in the bupivacaine group (148 ± 6 mm Hg) 30 s after injection. After the termination of seizures, the mean systolic and diastolic arterial pressure returned to predrug control values and remained there for the duration of the experiment.

Both treatment groups showed no significant decrease in mean pH values concurrent with seizure activity. Arterial P_{O_2} and P_{CO_2} remained unchanged in both groups during the period before institution of mechanical respiration (Tables 1 and 2).

Mean peak whole blood bupivacaine and ropivacaine concentrations averaged 3.18 ± 0.21 μ g/mL and 4.12 ± 0.88 μ g/mL, respectively, 30 s after drug injection. No differences in local anesthetic concentrations in the blood were seen between groups at any sampling interval (Figure 1).

Control lactate concentrations averaged 1.31 ± 0.11 mmol/L in the bupivacaine group and 1.03 ± 0.10 mmol/L in the ropivacaine group. These values are similar to those previously reported in awake dogs (15). During the convulsive period, lactate concentrations significantly increased to 3.40 ± 0.65 mmol/L in the bupivacaine group and 3.08 ± 0.42 mmol/L in the ropivacaine group. Lactate concentrations returned toward control values relatively slowly after control of seizures. There was no significant difference in lactate concentration between the two groups of dogs at any sampling interval (Figure 2).

Table 1. Cardiovascular Effects of Intravenous Bupivacaine in the Dog

Bupivacaine CD (4.3 mg/kg)	Predrug control	End of injection	+30 s	+1 min	+3 min
Heart rate (beats/min)	107 ± 5	132 ± 7 23%	165 ± 9 ^a 54%	150 ± 7 ^a 40%	120 ± 8 12%
PR interval (ms)	96 ± 3	96 ± 4 0% (n = 3)	105 ± 5 9% (n = 4)	112 ± 8 17% (n = 5)	112 ± 5 ^b 17% (n = 5)
QRS interval (ms)	52 ± 1	64 ± 8 23% (n = 3)	68 ± 5 ^b 31% (n = 4)	70 ± 5 ^a 35% (n = 5)	66 ± 6 27% (n = 5)
QT interval (ms)	215 ± 7	213 ± 7 -0.9% (n = 3)	225 ± 13 5% (n = 4)	248 ± 5 15% (n = 5)	274 ± 14 ^a 27% (n = 5)
Systolic blood pressure (mm Hg)	167 ± 3	202 ± 7 ^a 21%	200 ± 9 ^a 20%	185 ± 10 ^b 11%	188 ± 10 13%
Diastolic blood pressure (mm Hg)	99 ± 2	129 ± 12 ^b 30%	121 ± 6 ^a 22%	139 ± 11 ^a 40%	136 ± 8 ^a 37%
Mean arterial pressure (mm Hg)	122 ± 2	153 ± 10 ^b 25%	148 ± 6 ^a 21%	154 ± 10 ^a 26%	155 ± 10 ^a 27%
Respirations/min	71 ± 12 (n = 23)	58 ± 28 -18% (n = 3)	47 ± 3 -34%	21 ± 3 -70.0% (n = 3)	20 ± 3 -72%
Pao ₂ (mm Hg)	87 ± 2 (n = 12)	—	94 ± 3 8%	75 ± 10 -14%	418 ± 51 ^b 380%
Paco ₂ (mm Hg)	37 ± 1 (n = 12)	—	34 ± 3 -8%	41 ± 4 11%	37 ± 6 0%
pH (U)	7.42 ± 0.01 (n = 12)	—	7.42 ± 0.02 0%	7.36 ± 0.02 ^b -0.8%	7.38 ± 0.04 -0.5%

CD, convulsant dose; Pao₂, arterial O₂ tension; Paco₂, arterial CO₂ tension.

n = 24 for predrug control unless otherwise noted in parentheses.

n = 6 for all others unless otherwise noted in parentheses.

Barbiturate administered after the +30-s data were collected, i.e., +1 and +3 min, are after intravenous barbiturate.

^aSignificantly different from predrug control, *P* < 0.01.^bSignificantly different from predrug control, *P* < 0.05.

The epinephrine and norepinephrine control values in both treatment groups were similar and comparable to previously reported values for the dog (16). Epinephrine concentrations increased significantly in the bupivacaine group from 298 ± 91 pg/mL to 2577 ± 363 pg/mL, and in the ropivacaine group from 195 ± 18 pg/mL to 1970 ± 262 pg/mL during the convulsive period. Norepinephrine concentrations also increased significantly from 444 ± 63 pg/mL to 1767 ± 178 pg/mL in the bupivacaine group and from 315 ± 40 pg/mL to 1433 ± 255 pg/mL in the ropivacaine group. There was no significant difference between drug treatment groups (Figures 3 and 4).

Both epinephrine and norepinephrine concentrations decreased rapidly after the control of seizures and by 3 min after injection of local anesthetic, mean concentrations were similar to the control values.

The Supraconvulsant Dose

No significant difference in any predrug control values existed between the two groups in this portion of the study.

Convulsions following administration of the supraconvulsant dose (2 × CD) of ropivacaine (9.8 mg/kg) were rapidly terminated by intravenous thiamylal (10 mg/kg), after which dogs were intubated and mechanically ventilated with oxygen-enriched air. No other resuscitative therapy was required in 83% of the dogs in this group. In one animal, mean arterial blood pressure decreased rapidly from 200 to 88 mm Hg. Because of the rapidly decreasing arterial blood pressure, intravenous epinephrine (0.75 mg) was administered, which resulted in an increase in mean arterial blood pressure to 280 mm Hg and nodal or ventricu-

Table 2. Cardiovascular Effects of Intravenous Ropivacaine in the Dog

Ropivacaine CD (4.9 mg/kg)	Predrug control	End of injection	+30 s	+1 min	+3 min
Heart rate (beats/min)	112 ± 5	113 ± 14 0.9%	173 ± 15 ^a 54%	163 ± 10 ^a 46%	119 ± 10 6%
PR interval (ms)	95 ± 2	113 ± 7 19% (n = 3)	100 ± 0 5% (n = 3)	104 ± 8 10% (n = 5)	108 ± 5 14% (n = 5)
QRS interval (ms)	50 ± 1	56 ± 4 12% (n = 3)	67 ± 10 34% (n = 3)	66 ± 6 ^b 32% (n = 5)	56 ± 3 ^b 12% (n = 5)
QT interval (ms)	211 ± 5	233 ± 7 ^b 10% (n = 3)	227 ± 13 8% (n = 3)	224 ± 12 6% (n = 5)	282 ± 10 ^b 34% (n = 5)
Systolic arterial pressure (mm Hg)	181 ± 2	231 ± 6 ^a 28%	233 ± 11 ^a 29%	221 ± 9 ^a 22%	203 ± 7 ^b 12%
Diastolic arterial pressure (mm Hg)	106 ± 2	154 ± 7 ^a 45%	153 ± 13 ^a 44%	151 ± 8 ^a 42%	143 ± 6 ^a 35%
Mean arterial pressure (mm Hg)	131 ± 2	179 ± 6 ^a 37%	180 ± 12 ^a 37%	175 ± 8 ^a 34%	163 ± 6 ^a 24%
Respirations/min	86 ± 13	104 ± 40 21% (n = 4)	48 ± 15 -44% (n = 4)	38 ± 5 -56% (n = 5)	25 ± 3 ^b -71%
Pao ₂ (mm Hg)	91 ± 1.4 (n = 12)	—	74 ± 8 -19% (n = 5)	177 ± 68 95%	338 ± 79 ^b 271%
Paco ₂ (mm Hg)	37 ± 0.6 (n = 12)	—	41 ± 3 11%	39 ± 2 +5%	35 ± 3 -5%
pH (U)	7.41 ± 0.01 (n = 12)	—	7.36 ± 0.03 -0.7%	7.35 ± 0.3 ^b -0.8% (n = 5)	7.38 ± 0.02 -0.4%

CD, convulsant dose; Pao₂, arterial O₂ tension; Paco₂, arterial CO₂ tension.

n = 24 for predrug control unless otherwise noted in parentheses.

n = 6 for all others unless otherwise noted in parentheses.

Barbiturate administered after the +30-s data were collected, i.e., +1 and +3 min, are after intravenous barbiturate.

^aSignificantly different from predrug control, *P* < 0.01.^bSignificantly different from predrug control, *P* < 0.05.

lar tachycardia at a rate of 180 beats/min. Bretylium (20 mg/kg) was administered intravenously and the arrhythmia subsequently converted to a bigeminal rhythm and then to a normal sinus rhythm within 20 min. The trachea of this animal was subsequently extubated, and recovery proceeded with no apparent adverse effects. A second dog treated with ropivacaine showed two brief episodes of ectopy consisting of seven premature ventricular contractions within a 1-min period. Before therapy could be initiated, normal sinus rhythm spontaneously returned.

Convulsions in all dogs receiving 2 × CD of bupivacaine (8.6 mg/kg) were also successfully terminated with thiamylal, and respiratory support was instituted. Sixty-seven percent of the dogs (4 of 6) required no additional treatment and recovered uneventfully. Two dogs in this group, however, died despite resuscitative measures. Hypotension devel-

oped in both animals within 1 min of the injection. Ventricular arrhythmias were also observed and ultimately ventricular fibrillation. Cardiovascular resuscitative measures consisted of multiple doses of epinephrine (0.75 mg IV), manual chest compressions, bretylium (20 mg/kg IV), atropine (0.8 mg), and in one case several attempts at direct current cardioversion. Resuscitative measures continued for 7.5 min in one dog and for 30 min in the other. Resuscitative measures were terminated when ventricular fibrillation persisted for 5 min or longer and no arterial blood pressure existed for five consecutive minutes.

Heart rate increased to 161 ± 12 beats/min (30%) in the bupivacaine group during seizures and 167 ± 8 beats/min (48%) in the ropivacaine group (Tables 3 and 4). Only the increase seen in the ropivacaine group was significant, but there was no difference between groups at any time interval. After seizures

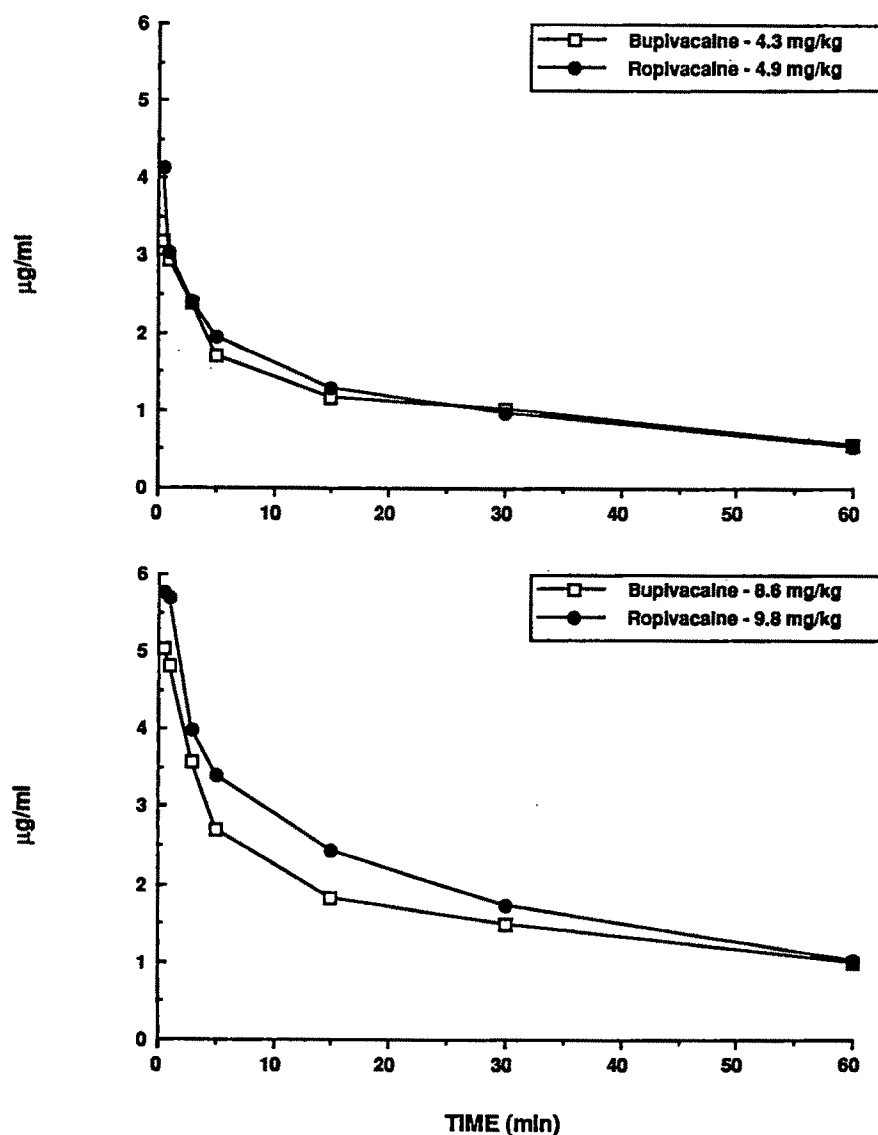


Figure 1. Local anesthetic concentrations in whole blood (SEM omitted for clarity). At $2 \times CD$: bupivacaine, $n = 4$; ropivacaine, $n = 5$.

were controlled, heart rates returned to predrug control levels and remained there for the balance of the experiment.

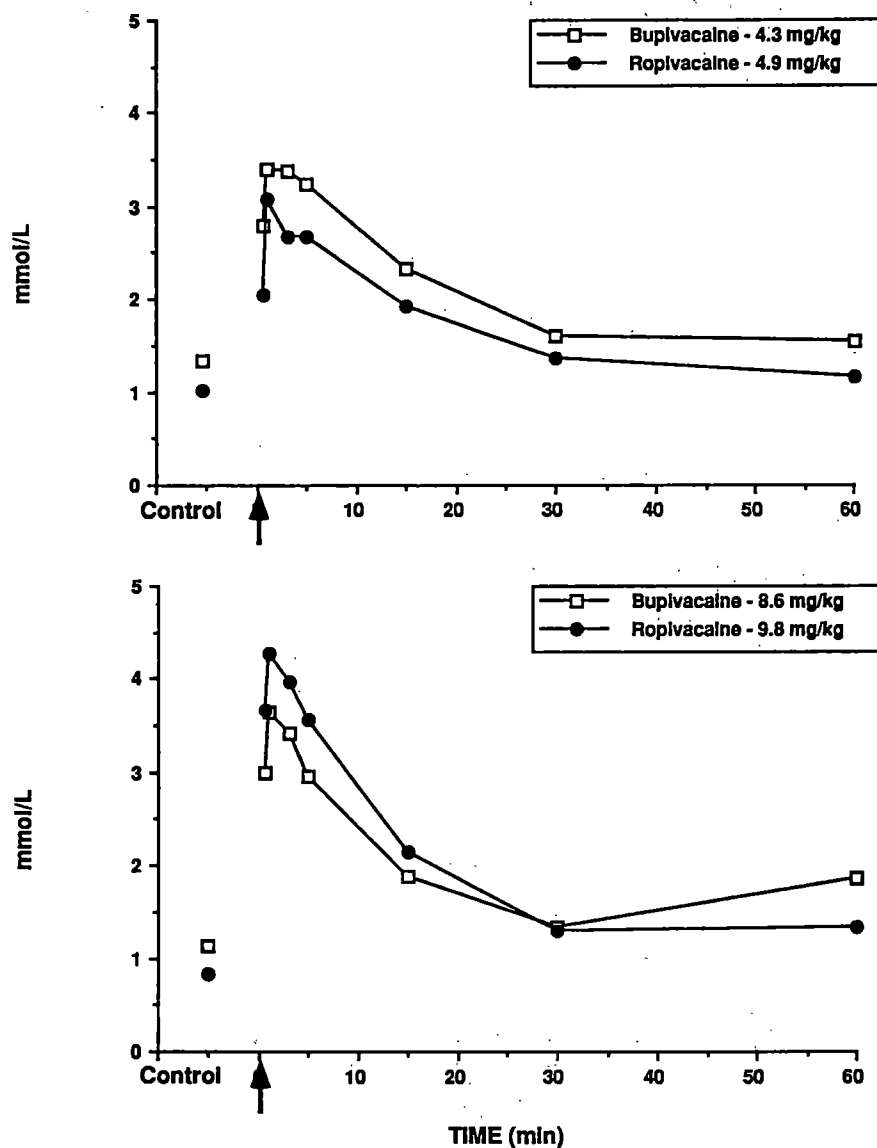
Administration of local anesthetic produced no significant changes in PR intervals in the surviving animals and there was no difference between groups (Tables 3 and 4). Significant increases of a similar magnitude in the QRS interval occurred in both treatment groups. Significant increases in the QT interval also were seen in both groups after drug injection. There were no significant differences between groups at any time interval.

The four survivors in the bupivacaine group showed an average decrease of 14% in mean arterial blood pressure at 1 min after ending the injection, which was not significant (Tables 3 and 4). Conversely, an increase of 32% was seen in the ropiv-

acaine group at this time. The change in the bupivacaine group was significantly different from that of the ropivacaine group. Mean arterial blood pressure values for the balance of the study were not significantly different between groups nor were they different from control values.

The pH_a in the bupivacaine group remained unchanged during seizure activity (Table 3). In the ropivacaine group, pH_a decreased from a control value of 7.40 ± 0.01 U to 7.37 ± 0.04 U, which occurred during seizure activity. The pH_a in this group reached a low value of 7.32 ± 0.04 U after the control of seizures. However, this change in pH_a was not significant (Table 4). There were no significant differences between groups at any time interval. Arterial PO_2 and PCO_2 did not change during seizure activity.

Figure 2. Lactate concentrations in venous blood (SEM omitted for clarity). Arrow indicates time of drug injection. Concentrations in both drug groups at both doses are significantly higher than control values until +15 min. At $2 \times$ CD: bupivacaine, $n = 4$; ropivacaine, $n = 5$.



The mean peak anesthetic concentrations in whole blood in surviving animals were $5.04 \pm 0.13 \mu\text{g/mL}$ for bupivacaine and $5.75 \pm 0.23 \mu\text{g/mL}$ for ropivacaine (Figure 1). In the two animals that died, the peak bupivacaine concentrations were 11.6 and 10.0 $\mu\text{g/mL}$. The peak ropivacaine blood concentration was 8.57 $\mu\text{g/mL}$ in the one animal in the ropivacaine group that was treated with epinephrine and bretylium. Ropivacaine blood concentrations decreased rapidly in this animal after effective control of blood pressure. In the two bupivacaine-treated animals that died, blood bupivacaine concentrations had only decreased from 11.6 to 11.0 $\mu\text{g/mL}$ and from 10.0 to 6.5 $\mu\text{g/mL}$ at the time that resuscitative efforts were terminated.

Mean lactate concentrations increased significantly from 1.17 ± 0.10 to $3.64 \pm 0.35 \text{ mmol/L}$ in the sur-

living bupivacaine-treated animals and from 0.87 ± 0.11 to $4.27 \pm 0.56 \text{ mmol/L}$ in the ropivacaine-treated animals not requiring cardiovascular therapy. Lactate concentrations decreased slowly, returning toward predrug control values at 30 and 60 min after drug injection (Figure 2). In the two bupivacaine-treated dogs that died, lactate concentrations continued to increase until resuscitative efforts were discontinued. However, with the exception of the final sample taken in one of these animals, lactate concentrations were within the range seen in surviving animals.

In the animals in both groups that were not treated with epinephrine, the concentrations of epinephrine and norepinephrine before and after drug administration were similar to those seen in the first portion of this study (Figures 3 and 4).

Maximum epinephrine concentrations of approxi-

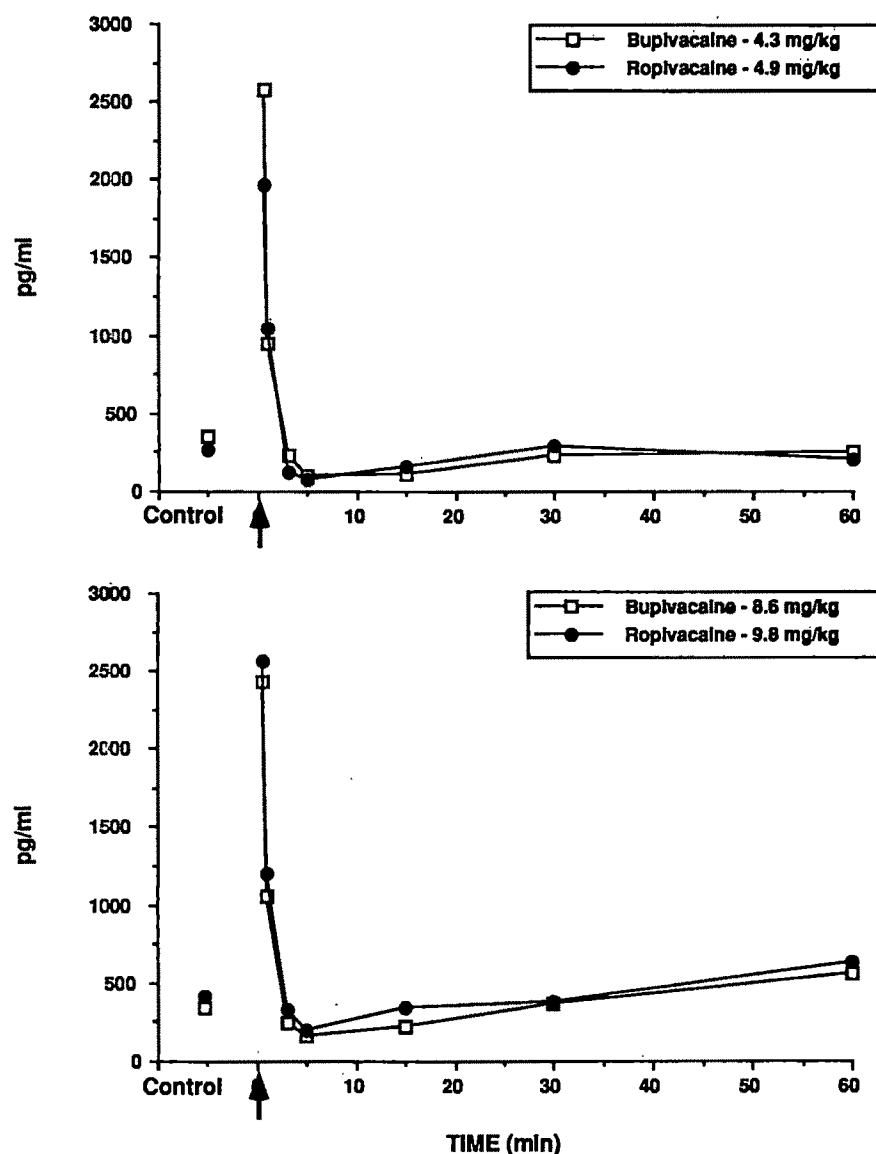


Figure 3. Epinephrine concentrations in arterial serum (SEM omitted for clarity). Arrow indicates time of drug injection. Concentrations significantly higher compared to control at +30 s and 1 min for bupivacaine at both doses, and at +30 s for ropivacaine at both doses. At $2 \times$ CD: bupivacaine, $n = 4$; ropivacaine, $n = 5$.

mately 3 $\mu\text{g/mL}$ occurred in nonsurviving bupivacaine-treated animals given epinephrine during resuscitative efforts. In the ropivacaine-treated animal that received intravenous epinephrine, a peak concentration of 1.2 $\mu\text{g/mL}$ of epinephrine was measured.

Discussion

Previous investigations involving the treatment of bupivacaine-induced cardiotoxicity have been carried out in cats (12), dogs (9,10), and sheep (11). Some of these studies were conducted in animals that were either anesthetized, had a thoracotomy, were rendered hypoxic, had ventricular arrhythmias produced by electric pacing, or had some combination of

these conditions. In some of the reports, the animals received an intravenous infusion of bupivacaine as opposed to a bolus injection (10,12). Successful resuscitation was reported in all but one of these studies by a combination of direct cardiac massage, pharmacologic intervention (e.g., epinephrine, bretylium, atropine), mechanical ventilation, and direct current cardioversion using internal paddles directly on the heart. The current study was designed to more closely mimic a possible clinical situation. The results are similar to those reported by Chadwick (12) where 20% of the cats rendered cardiotoxic with bupivacaine could not be resuscitated. In the current study, 33% of the dogs were not successfully resuscitated. However, other resuscitative methods may have proven more efficacious.

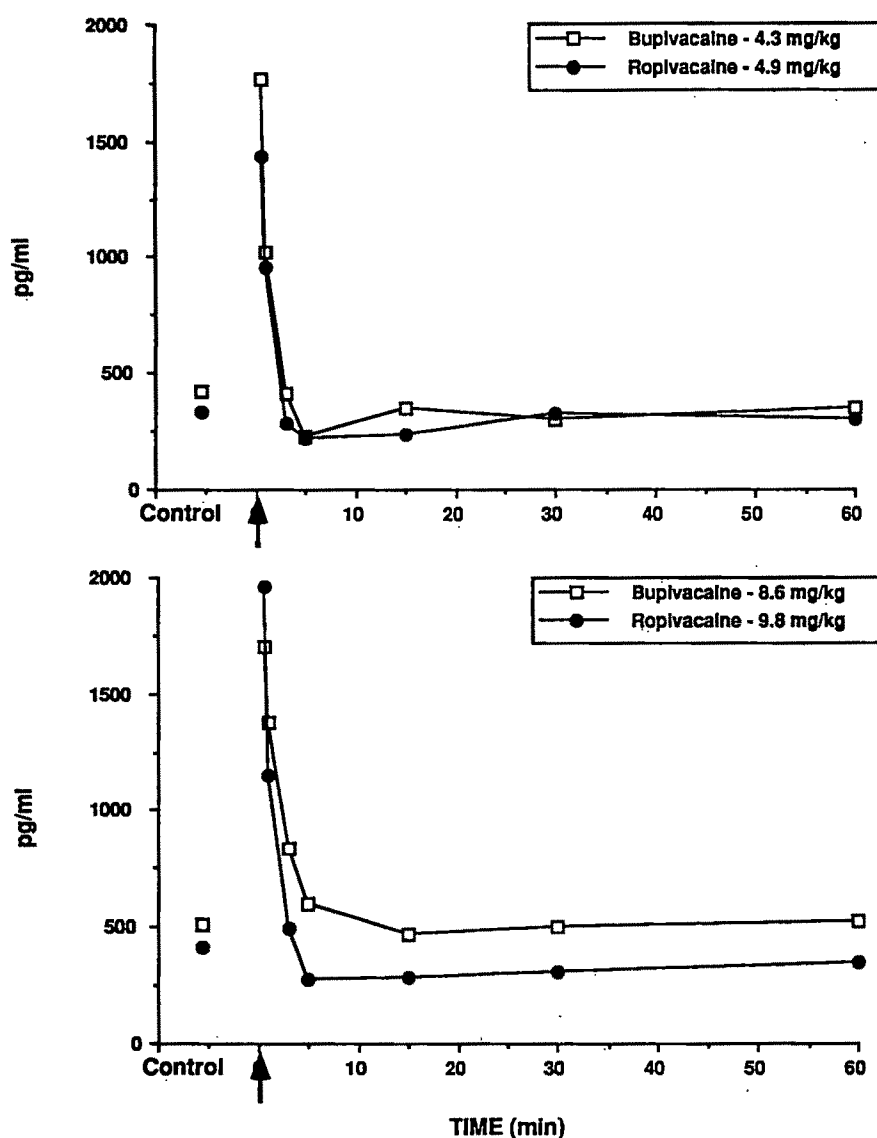


Figure 4. Norepinephrine concentrations in arterial serum (SEM omitted for clarity). Arrow indicates time of drug injection. Concentrations significantly higher compared with control at +30 s only for both drugs at both doses. At $2 \times$ CD: bupivacaine, $n = 4$; ropivacaine, $n = 5$.

In a previous study with a similar experimental protocol and where no early resuscitative efforts were attempted, a significantly greater number of dogs (five of six, 83%) receiving two times the CD of bupivacaine died as compared with those receiving ropivacaine (one of six, 17%) (6). Additionally, the incidence of arrhythmias in the bupivacaine group (five of six, 83%) was also significantly higher than in the ropivacaine group (two of six, 33%). In the current study, the early institution of resuscitative efforts reduced the mortality rate from 83% to 33% in the bupivacaine group and from 17% to 0% in the ropivacaine group. The incidence of ventricular arrhythmias in the bupivacaine group was also reduced from 83% to 33%. The frequency of arrhythmias in the ropivacaine group remained unchanged at 33%. The early institution of therapy, in the form of control

of seizures and support of respiration, resulted in a reduction of mortality in both treatment groups and a reduction in arrhythmias in the bupivacaine group when compared with the previously reported study.

The rapid production of acidosis and hypoxia after local anesthetic-induced toxicity has been documented in humans and dogs (6,17,18). Acidosis was observed in the current study after the onset of seizure activity. However, arterial P_{CO_2} and P_{O_2} were not altered. Lactic acid concentrations rose significantly during seizures, indicating that the acidosis was metabolic in origin. After the control of seizures, lactic acid concentrations remained significantly elevated for approximately 30 min. This may be due to the large lactic acid production during seizures being ineffectually removed from the circulation as a result of reduced hepatic blood flow. Also, bupivacaine

Table 3. Cardiovascular Effects of Intravenous Bupivacaine in the Dog

Bupivacaine SC (8.6 mg/kg)	Predrug control	End of injection	+30 s	+1 min	+3 min
Heart rate (beats/min)	124 ± 4	144 ± 3 16% (n = 4)	161 ± 12 30% (n = 4)	154 ± 7 24% (n = 4)	139 ± 10 12% (n = 4)
PR interval (ms)	95 ± 3	125 ± 5 ^a 32% (n = 4)	115 ± 10 ^b 21% (n = 4)	115 ± 5 ^b 21% (n = 4)	117 ± 3 ^a 23% (n = 3)
QRS interval (ms)	49 ± 3	71 ± 4 45% (n = 4)	75 ± 5 ^b 53% (n = 4)	83 ± 6 ^b 69% (n = 4)	72 ± 4 ^a 47% (n = 3)
QT interval (ms)	201 ± 3	220 ± 0 ^a 9% (n = 4)	230 ± 6 ^a 14% (n = 4)	245 ± 5 ^a 22% (n = 4)	297 ± 12 ^a 48% (n = 3)
Systolic arterial pressure (mm Hg)	180 ± 6	170 ± 17 -6% (n = 4)	164 ± 9 -9% (n = 4)	155 ± 11 -14% (n = 4)	178 ± 17 -1% (n = 4)
Diastolic arterial pressure (mm Hg)	107 ± 6	90 ± 16 ^b -16% (n = 4)	99 ± 6 -7% (n = 4)	108 ± 13 0.9% (n = 4)	142 ± 17 ^b 33% (n = 4)
Mean arterial pressure (mm Hg)	132 ± 6	116 ± 16 -12% (n = 4)	120 ± 7 -9.0% (n = 4)	114 ± 13 -14% (n = 4)	154 ± 17 17% (n = 4)
Respirations/min	63 ± 10	20 ± 4 ^b -68% (n = 2)	62 ± 18 -2% (n = 4)	22 ± 6 ^b -65% (n = 4)	17 ± 3 ^a -73% (n = 4)
Pao ₂ (mm Hg)	86 ± 2 (n = 12)	—	92 ± 7 7.0% (n = 4)	132 ± 32 53% (n = 4)	499 ± 23 ^a 480% (n = 4)
Paco ₂ (mm Hg)	35 ± 2 (n = 12)	—	31 ± 4 -11% (n = 4)	34 ± 4 -3% (n = 4)	33 ± 3 -6.0% (n = 4)
pH (U)	7.43 ± 0.01 (n = 12)	—	7.44 ± 0.04 0.1% (n = 4)	7.39 ± 0.03 ^b -0.5% (n = 4)	7.38 ± 0.02 -0.7% (n = 4)

SC, supraconvulsant dose; Pao₂, arterial O₂ tension; Pco₂, arterial CO₂ tension.

n = 24 for predrug control unless otherwise noted in parentheses.

n = 6 for all others unless otherwise noted in parentheses.

Barbiturate administered after the +30-s data were collected, i.e., +1 and +3 min, are after intravenous barbiturate.

^aSignificantly different from predrug control, *P* < 0.01.^bSignificantly different from predrug control, *P* < 0.05.

infusions in humans producing clinically achieved blood concentrations (1.8 µg/mL) have been reported to significantly increase lactate levels (19), and this too could account for the prolonged elevation of lactate levels in the current study.

The use of epinephrine in the treatment of cardiovascular collapse after bupivacaine overdose is also controversial. Very high doses of epinephrine (30–1020 µg/kg IV) are an effective treatment of cardiac arrest from bupivacaine overdose in rats (20). Epinephrine was also part of the successful resuscitative regimen in the cat and dog studies (9,12). However, epinephrine was not of value in attempts to resuscitate sheep (11). Multiple doses of epineph-

rine were not effective in the treatment of bupivacaine-induced cardiotoxicity in the two dogs that died in the current studies. Moreover, the one animal in the ropivacaine group receiving epinephrine developed ventricular tachycardia and hypertension. Thus, other vasopressor drugs with less direct cardiac effects, such as phenylephrine, may be more beneficial than epinephrine in the treatment of local anesthetic-induced hypotension.

In summary, our results are consistent with a previous study in dogs (6) that indicated that ropivacaine is less cardiotoxic and less arrhythmogenic than bupivacaine. The experimental protocol used in that study was similar to the one reported currently

Table 4. Cardiovascular Effects of Intravenous Ropivacaine in the Dog

Ropivacaine SC (9.8 mg/kg)	Predrug control	End of injection	+30 s	+1 min	+3 min
Heart rate (beats/min)	113 ± 5	160 ± 11 ^a 42%	167 ± 8 ^a 48%	153 ± 5 ^a 35%	130 ± 21 15%
PR interval (ms)	89 ± 2	126 ± 14 42% (n = 2)	107 ± 7 ^a 20% (n = 3)	106 ± 6 ^a 19% (n = 5)	10 ± 5 ^b 24% (n = 5)
PR segment (ms)	44 ± 2	64 ± 16 45% (n = 2)	51 ± 5 16% (n = 3)	52 ± 7 18% (n = 5)	52 ± 7 18% (n = 5)
QRS interval (ms)	44 ± 2	80 ^a 82% (n = 2)	80 ± 0 ^b 82% (n = 3)	76 ± 5 ^b 73% (n = 5)	63 ± 6 43% (n = 5)
QT interval (ms)	201 ± 5	200 -0.5% (n = 2)	207 ± 7 ^a 3% (n = 3)	236 ± 8 ^a 17% (n = 5)	258 ± 10 ^a 28% (n = 5)
Systolic arterial pressure (mm Hg)	185 ± 4	191 ± 18 3%	212 ± 12 15%	225 ± 42 22%	190 ± 14 3%
Diastolic arterial pressure (mm Hg)	103 ± 3	103 ± 12 0%	138 ± 14 34%	142 ± 24 38%	130 ± 10 26%
Mean arterial pressure (mm Hg)	129 ± 3	132 ± 13 2%	163 ± 11 26%	170 ± 29 32%	150 ± 11 16%
Respirations/min	53 ± 7 (n = 23)	65 ± 2 23% (n = 2)	48 ± 19 -9% (n = 4)	20 ± 11 -62% (n = 5)	23 ± 2 -57%
Pao ₂ (mm Hg)	90 ± 2 (n = 12)	—	86 ± 11 -4% (n = 5)	284 ± 74 216% (n = 5)	412 ± 35 ^b 358%
Paco ₂ (mm Hg)	35 ± 1 (n = 12)	—	33 ± 6 -6% (n = 5)	35 ± 5 0% (n = 5)	35 ± 6 0%
pH (U)	7.41 ± 0.01 (n = 12)	—	7.37 ± 0.04 -0.5% (n = 5)	7.34 ± 0.04 -0.5% (n = 5)	7.32 ± 0.04 -1%

SC, supraconvulsant dose; Pao₂, arterial O₂ tension; Paco₂, arterial CO₂ tension.

n = 24 for predrug control unless otherwise noted in parentheses.

n = 6 for all others unless otherwise noted in parentheses.

Barbiturate administered after the +30-s data were collected, i.e., +1 and +3 min, are after intravenous barbiturate.

^aSignificantly different from predrug control, *P* < 0.05.^bSignificantly different from predrug control, *P* < 0.01.

except no early resuscitative action was taken. Bupivacaine was reported to be significantly more lethal than ropivacaine. In the current study, the early control of seizures and support of respiration resulted in a reduction of mortality as compared with the previous study. No significant difference in mortality existed between bupivacaine and ropivacaine in the current study. The mechanism by which the control of seizures and support of respiration aided in the survival of bupivacaine- or ropivacaine-intoxicated dogs is unclear. It is possible that the reduction in circulating catecholamines secondary to seizure control may play an important role. The cardiovascular depression produced by ropivacaine was of a less severe nature than that produced by bupivacaine and

therefore may be more easily managed. Only one protocol of resuscitative treatment was studied. It is possible that other methods of resuscitation may prove more efficacious.

Our study demonstrated that there was no significant difference in mortality between the two drug groups. The rapid aggressive treatment of seizures and support of respiration appears to be of importance in the management of local anesthetic toxicity.

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Heart Rate Responses to Body Tilt During Spinal Anesthesia

Yukinobu Anzai, MD, and Toshiaki Nishikawa, MD

Department of Anesthesia, Obihiro Kousei General Hospital, Obihiro City, Hokkaido, and the Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba City, Ibaraki, Japan

To evaluate whether low-pressure baroreceptors located in the right atrium could affect the heart rate (HR) during spinal anesthesia, the authors determined the effects of right atrial pressure changes associated with body tilt on HR in 40 unpremedicated patients. Ten-degree head-up body tilt produced significant increases in HR of 6 ± 1 and 6 ± 1 beats/min (mean \pm SE, $P < 0.01$) and significant decreases in systolic arterial pressure of 2.8 ± 0.9 and 6.6 ± 1.7 mm Hg ($P < 0.01$) during low ($T-10 \pm 0.2$, $n = 20$) and high ($T-4 \pm 0.2$, $n = 20$) analgesic levels of tetracaine spinal anesthesia, respectively. Ten-degree head-down body tilt caused significant decreases in HR without significant changes in systolic arterial

pressure during spinal anesthesia. The reflex HR responses to body tilt were similar between low and high levels of spinal anesthesia and were preserved after administration of sedatives. The magnitudes of changes in right atrial pressure associated with body tilt were similar during spinal anesthesia and after sedation. These findings suggest that HR responses to head-up body tilt are mediated mainly by arterial baroreceptors even in the face of decreased venous return during low or high levels of spinal anesthesia and that light sedation does not impair this reflex HR response.

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Sinus bradycardia is one of the well-known cardiovascular effects during spinal anesthesia, which could potentially result in a sudden cardiac arrest (1-7). The cause of this bradycardia has been attributed to either preganglionic block of cardiac accelerator fibers or decrease in venous return to the heart, or both (1). Reduced venous return could predispose the heart rate (HR) to decrease during spinal anesthesia (1), although this reflex HR response is presumably mediated by an intrinsic chronotropic stretch receptor located primarily in the right atrium. Baron et al. (8) found that cardiac vagal tone is enhanced mainly through a reduced venous return during lumbar epidural anesthesia in humans. However, HR variability response can be mediated through atrial and/or arterial baroreceptors.

The knowledge of cardiovascular responses to body tilt during spinal anesthesia, which is invariably accompanied by changes in venous return to the heart, is of clinical relevance because there may be no alternatives to head-up or head-down body tilt for

obtaining an appropriate analgesic level. However, there have been no clinical studies examining the potential effect of changes in the right atrial pressure (RAP) on the HR during spinal anesthesia. Thus, we sought to investigate the role of body tilt-induced alterations of venous return in the control of HR during low or high analgesic levels of spinal anesthesia.

Methods

The protocol was approved by our Institutional Human Studies Committee. Forty unpremedicated patients, ASA physical status I, scheduled to have spinal anesthesia for their surgical procedures were studied after written informed consent was obtained from each patient. They had no cardiovascular or neurologic disorders and were taking no drugs that have any influences upon the cardiovascular system.

Heart rate was monitored by lead II of the electrocardiogram and recorded on a beat-to-beat basis by a cardi tachometer (AT-601G, Nihon-Kohden, Tokyo). A 20-gauge cannula was inserted into the radial artery under local anesthesia with lidocaine to permit continuous monitoring and recording of systolic (SAP) and diastolic (DAP) arterial pressures. Right atrial pressure was monitored from a catheter in-

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Address correspondence to Dr. Nishikawa, Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba City, Ibaraki 305, Japan.

serted into the right atrium via a basilic vein under local anesthesia. Position of the right atrial catheter was confirmed by the characteristic waveforms. The radial arterial and right atrial catheters were connected to calibrated transducers (Statham P50; Gould, Cleveland, Ohio). The transducer was taped to the chest wall so that the zero reference was leveled at the right atrium. All pressures were obtained at end expiration. Cardiac output (CO) was continuously measured by bioimpedance cardiography (NCCOM-3; Bomed Medical Manufacturing, Irvine, Calif.). Real-time values of CO obtained by impedance cardiography were averaged over 10 beats by a computer (PC-286LE; Epson, Tokyo). With regard to the reliability of the bioimpedance cardiography, a good correlation with conventional thermodilution techniques has been reported (9). Derived hemodynamic variables included mean arterial pressure ($MAP = [SAP + 2 DAP]/3$) and systemic vascular resistance ($SVR = [MAP - RAP] \times 80/CO$).

After a resting period of 30 min, baseline hemodynamic measurement was made while the patient was placed in the supine horizontal position. Then the patient was changed from the horizontal position to either 10° head-up or head-down body tilt. The hemodynamic data during body tilt were obtained when the RAP and HR had stabilized for at least 30 s in each body position.

After putting the patient in the lateral position and sterilizing the lumbar region of the skin, spinal anesthesia was induced with a 25-gauge needle at the L3-4 intervertebral space using 2.0 or 3.0 mL of 0.5% tetracaine solution in 10% dextrose with 0.025% phenylephrine. The patient was immediately placed in the supine horizontal position. At more than 20 min after the subarachnoid injection of tetracaine solution, the upper analgesic level to pin-prick was confirmed to have reached and fixed around the dermatome up to T-10 and T-4 in the low level ($n = 20$) and high level ($n = 20$) of spinal anesthesia, respectively. The same hemodynamic measurements were repeated with the supine horizontal position and 10° head-up or head-down body tilt.

Thereafter, half of the patients ($n = 10$) in each group received 15 mg of pentazocine and 10 mg of diazepam intravenously. After sedation and a stable hemodynamic period of more than 10 min were obtained with the supine horizontal position, the last set of measurements was made to observe the hemodynamic responses to 10° head-up or head-down body tilt during spinal anesthesia supplemented with sedatives.

The order of performing head-up or head-down body tilt was randomized in each patient before and during spinal anesthesia and after sedation. The duration of head-up or head-down body tilt was about 90 s throughout the experiment. Lactated

Table 1. Characteristics of Patients

	Low spinal anesthesia ($n = 20$)	High spinal anesthesia ($n = 20$)
Analgesic level	T-10 \pm 0.2	T-4 \pm 0.2*
Age (yr)	39 \pm 2	38 \pm 2
Height (cm)	166 \pm 2	160 \pm 1
Weight (kg)	67 \pm 2	63 \pm 1
Sex (M/F)	12/8	10/10

Values are mean \pm SE.

* $P < 0.01$ compared with low spinal anesthesia.

Ringer's solution was administered through a peripheral intravenous catheter at a rate of $10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ during the study. No vasopressors were administered intravenously in any patients of the two groups.

All values were expressed as mean \pm SE. Statistical analyses of the results were performed by analysis of variance with repeated measurements followed by Student's *t*-test. *P* values less than 0.05 were considered to be statistically significant.

Results

Table 1 shows the mean values of upper analgesic level to pin-prick (dermatome) in the two groups of low and high spinal anesthesia. The patients in both groups were similar with respect to age, height, weight, and sex distribution (Table 1). Baseline hemodynamic data obtained with the supine horizontal position (before body tilt) are shown in Table 2. A significant HR increase was observed in low spinal anesthesia but not in high spinal anesthesia as compared with the prespinal value. Both low and high spinal anesthesia resulted in significant decreases in RAP, SAP, DAP, and MAP ($P < 0.01$). Cardiac output showed no significant changes, whereas SVR decreased significantly ($P < 0.05$) after spinal anesthesia in both groups. After sedation, CO decreased and SVR increased significantly when compared with prespinal and postspinal values in the two groups ($P < 0.01$). The significant increase in RAP ($P < 0.05$) was noted after sedation only in high spinal anesthesia. However, there were no significant differences between both low and high spinal anesthesia groups in the three stages of observations.

Figure 1 shows representative hemodynamic responses to positional change from supine horizontal to 10° head-up body tilt in a patient with T-10 upper analgesic level of spinal anesthesia. Ten-degree head-up body tilt produced an increase in HR along with decreased RAP.

Before spinal anesthesia, head-up body tilt caused

Table 2. Baseline Hemodynamic Data During Supine Horizontal Position

		Prespinal anesthesia (n = 20)	Postspinal anesthesia (n = 20)	After sedation (n = 10)
HR (beats/min)	Low spinal	67 ± 2	70 ± 2 ^a	68 ± 2
	High spinal	72 ± 2	72 ± 3	65 ± 1
RAP (mm Hg)	Low spinal	3.4 ± 0.2	2.2 ± 0.2 ^b	2.5 ± 0.3
	High spinal	3.3 ± 0.1	2.0 ± 0.1 ^b	3.1 ± 0.2 ^c
SAP (mm Hg)	Low spinal	125 ± 3	116 ± 3 ^b	115 ± 3
	High spinal	122 ± 3	108 ± 3 ^b	115 ± 3
DAP (mm Hg)	Low spinal	71 ± 2	64 ± 2 ^b	65 ± 2
	High spinal	72 ± 2	64 ± 2 ^b	65 ± 2
MAP (mm Hg)	Low spinal	89 ± 2	81 ± 2 ^b	82 ± 2 ^a
	High spinal	89 ± 2	79 ± 2 ^b	82 ± 2
CO (L/min)	Low spinal	4.5 ± 0.1	4.5 ± 0.1	4.0 ± 0.1 ^{b,d}
	High spinal	4.7 ± 0.2	4.5 ± 0.2	3.8 ± 0.1 ^{b,d}
SVR (dyne·s·cm ⁻⁵)	Low spinal	1538 ± 61	1433 ± 45 ^a	1609 ± 51 ^d
	High spinal	1500 ± 74	1415 ± 63 ^a	1674 ± 71 ^{b,d}

HR, heart rate; RAP, right atrial pressure; SAP, systolic arterial pressure; DAP, diastolic arterial pressure; MAP, mean arterial pressure; CO, cardiac output; SVR, systemic vascular resistance.

Values are mean ± SE.

^aP < 0.05 compared with prespinal value.

^bP < 0.01 compared with prespinal value.

^cP < 0.05 compared with postspinal value.

^dP < 0.01 compared with postspinal value.

There were no significant differences in the hemodynamic data between low and high spinal anesthesia.

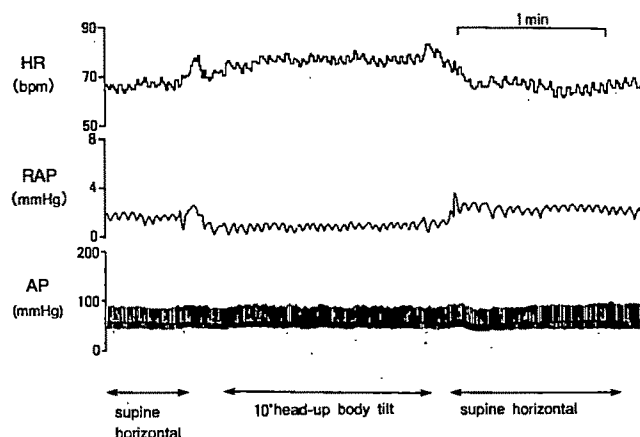


Figure 1. Representative polygraph tracings of HR, RAP, and arterial pressure (AP) during supine horizontal position and head-up body tilt in a patient with T-10 upper analgesic level of spinal anesthesia.

no significant changes in HR. However, a sustained significant HR increase was observed after head-up body tilt during low and high spinal anesthesia with or without sedation ($P < 0.01$, Figure 2). In contrast, head-down body tilt consistently resulted in significant decreases in HR before and during spinal anesthesia and after sedation (Figure 2). Right atrial pressure showed a significant decrease and increase during head-up and head-down body tilt, respectively ($P < 0.01$, Figure 3). The magnitudes of RAP changes associated with body tilt were similar before and during spinal anesthesia and after sedation.

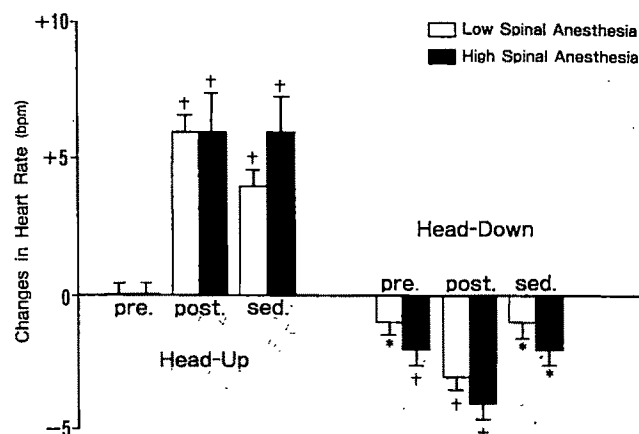


Figure 2. Changes in HR during head-up or head-down body tilt before (pre.) and during (post.) spinal anesthesia, and after sedation (sed.) in low or high spinal anesthesia. Values are mean ± SE. Baseline values before body tilt are given in Table 2. * $P < 0.05$, † $P < 0.01$ compared with the baseline value before body tilt.

Significant decreases in SAP were found when the patients were placed in head-up body tilt during spinal anesthesia and after sedation but not before spinal anesthesia (Figure 4). However, head-down body tilt caused no significant changes in SAP during three phases of the study in both low and high spinal anesthesia (Figure 4).

Head-up body tilt caused significant decreases in CO and increases in SVR before and during spinal anesthesia and after sedation (Figures 5 and 6). During head-down body tilt, the changes in CO and

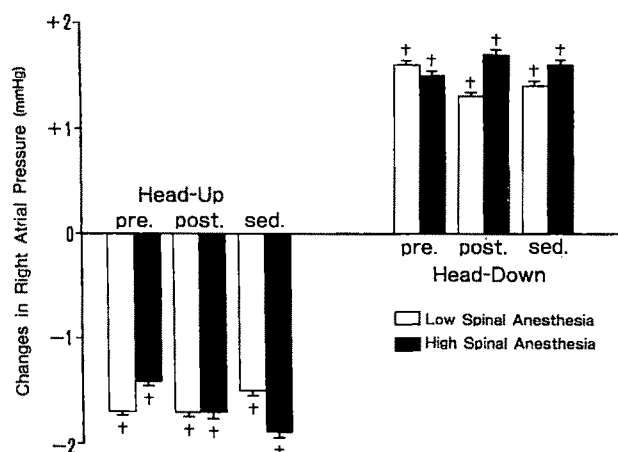


Figure 3. Changes in RAP during head-up or head-down body tilt before (pre.) and during (post.) spinal anesthesia, and after sedation (sed.) in low or high spinal anesthesia. Values are mean \pm SE. Baseline values before body tilt are given in Table 2. $^+P < 0.01$ compared with the baseline value before body tilt.

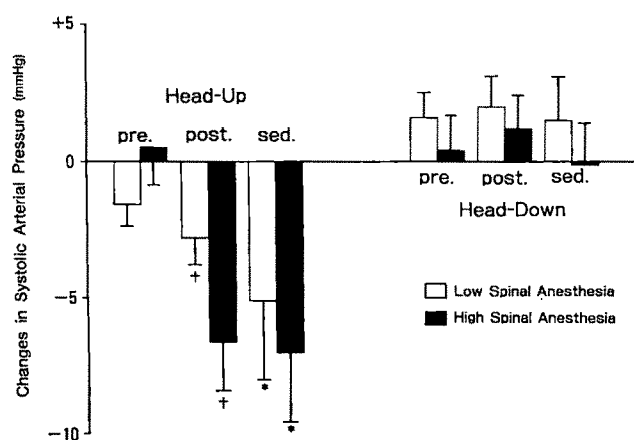


Figure 4. Changes in SAP during head-up or head-down body tilt before (pre.) and during (post.) spinal anesthesia, and after sedation (sed.) in low or high spinal anesthesia. Values are mean \pm SE. Baseline values before body tilt are given in Table 2. $^+P < 0.05$, $^{++}P < 0.01$ compared with the baseline value before body tilt.

SVR were in the opposite direction to those associated with head-up body tilt. Finally, there were no significant differences in the responses of HR, SAP, RAP, CO, and SVR to body tilt between the patients with low and high spinal anesthesia. The hemodynamic responses to body tilt after sedation were also similar to those before sedation during spinal anesthesia.

Discussion

This study demonstrated that 10° head-up body tilt during spinal anesthesia resulted in a significant HR increase along with significant decreases in RAP and SAP. This finding suggests that HR response to body

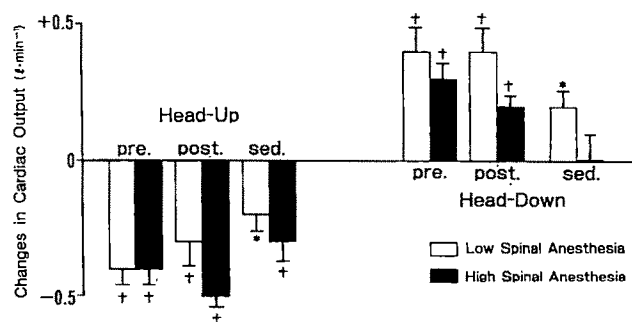


Figure 5. Changes in CO during head-up or head-down body tilt before (pre.) and during (post.) spinal anesthesia, and after sedation (sed.) in low or high spinal anesthesia. Values are mean \pm SE. Baseline values before body tilt are given in Table 2. $^+P < 0.05$, $^{++}P < 0.01$ compared with the baseline value before body tilt.

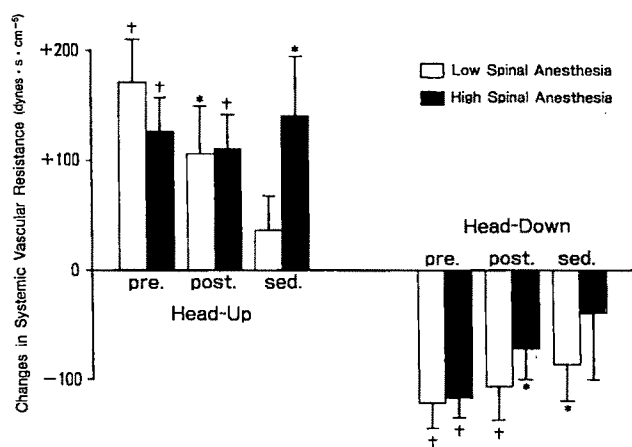


Figure 6. Changes in SVR during head-up or head-down body tilt before (pre.) and during (post.) spinal anesthesia, and after sedation (sed.) in low or high spinal anesthesia. Values are mean \pm SE. Baseline values before body tilt are given in Table 2. $^+P < 0.05$, $^{++}P < 0.01$ compared with the baseline value before body tilt.

tilt during spinal anesthesia is dependent on arterial baroreflex in the face of decreased venous return caused by head-up position. Absence of HR increase during 10° head-up body tilt before spinal anesthesia may suggest the possibility that spinal anesthesia-induced cardiovascular alterations could contribute to an increase in HR associated with head-up body tilt. Therefore, within the range of RAP decreases observed in this study, the inputs from the cardiopulmonary low-pressure receptors, which can sense slight changes in thoracic central blood volume, seem to play only a minor role in the reflex control of HR during spinal anesthesia.

The bradycardia associated with spinal anesthesia has been ascribed in part to an interruption of the efferent sympathetic cardiac accelerator fibers of T-1 through T-4 (1,10). In our patients with T-4 sensory (analgesic) level of high spinal anesthesia, most parts of the cardiac efferent sympathetic nerves might have

been blocked, as two spinal segments of differential sympathetic blockade exit above the level of sensory spinal blockade (11). Furthermore, although the mean sympathetic-sensory differential with tetracaine spinal anesthesia is more than six spinal segments, the authors suggested that the upper sympathetic blockade is only partial (12). Our results, indeed, showed that head-up body tilt induced similar HR increases during either low or high level of spinal anesthesia. These findings indicate that the T-4 sensory level of spinal anesthesia could not produce total sympathetic blockade and leave the reactivity of the upper parts of cardioaccelerator nerves intact to the same degree as in the T-10 level of spinal anesthesia.

The changes in RAP induced by head-up body tilt before spinal anesthesia were comparable to those after spinal anesthesia, which augment lower-body venous compliance owing to deprivation of the sympathetic tone (1). The reason for the similar decreases in RAP associated with head-up body tilt before and after spinal anesthesia is not known but may be related to the small degree of head-up body tilt. Cardiopulmonary low-pressure baroreceptors exert the tonic inhibitory effect on sympathetic outflow, and that unloading of these stretch receptors because of decreased venous return leads to sympathetic vasoconstriction in the forearm or splanchnic vascular bed without affecting HR (13,14). Because SVR increased in response to head-up body tilt without significant changes in SAP and HR from baselines before spinal anesthesia (Figures 2, 4, and 6), right atrial stretch receptors could be assumed to be unloaded during head-up body tilt despite the small decrease in RAP of approximately 2 mm Hg (Figure 3). Positive chronotropic responses to head-up body tilt during spinal anesthesia, therefore, suggest that negative chronotropic intrinsic cardiac reflex (1) or increased cardiac vagal tone (8,15) owing to reduced venous return was masked or overshadowed by arterial baroreflex during spinal anesthesia. Ecoffey et al. (16) have shown that positive chronotropic responses to hypotension induced by 30° head-up body tilt were impaired in elderly men, even when the upper level of epidural analgesia was below T-4. In contrast to the advanced age of the patients in their report, our patients are relatively young and healthy, which might in part account for the discrepancy between the HR responses to head-up body tilt. However, we cannot exclude the possibility that bradycardia might be induced by the steeper head-up body tilt during spinal anesthesia even in our relatively young patients, which could reduce the RAP beyond the range of the current study.

Aside from denervation of cardiac accelerator nerves and unloading of right atrial stretch baroreceptors owing to reduced venous return, paradoxical

Bezold-Jarisch reflex originating from the mechanoreceptors or chemoreceptors in the left ventricular wall has been suggested by Mackey et al. (7) as one of the possible mechanisms for reflex bradycardia during spinal anesthesia. They have speculated that a rapid decrease in ventricular volume could increase the activity of these ventricular wall receptors owing to vigorous ventricular contraction around the chamber of an abruptly reduced volume. However, our results could not confirm this mechanism, as the significant increase in HR ensued possibly from the decreased blood pressure, although the left ventricular volume would be reduced secondary to decreased venous return (17).

Although the contribution of sedative drugs to bradycardia during spinal anesthesia has been suggested (5,6), sedation exerted no significant effects on HR responses induced by body tilt in the current study (Figure 2). With regard to the intensity of sedation, intravenous administration of 15 mg of pentazocine and 10 mg of diazepam might be insufficient to produce intense sedation, because only relatively young and healthy unpremedicated patients were included in the current study. Indeed, some patients were in a sleeplike state, but they all responded immediately when spoken to. This slight degree of sedation achieved in our study might be related to only minimal influence of sedation on HR responses induced by body tilt during spinal anesthesia.

In agreement with previous studies, CO showed no significant changes after induction of spinal anesthesia (18-20), although a significant decrease in RAP of about 1 mm Hg was noted (Table 2). Thus, the slight but significant decrease in arterial pressure after spinal anesthesia can be ascribed to decreased SVR from baseline. Also, the significant decrease in CO after the administration of sedatives (Table 2) seems to be attributed to direct myocardial depression and/or reduced oxygen requirement. The magnitude of CO increase produced by head-down body tilt before or after spinal anesthesia (approximately 5%-8% of the value in the supine horizontal position) was compatible with previous studies examining the relationship between body positioning and cardiac performance (21,22).

Several previous investigators have demonstrated positive chronotropic responses to head-up body tilt associated with decreased CO and vasoconstriction in nonanesthetized humans (23-28). In the current study, we also noted significant increases in HR and SVR with CO decreases after head-up body tilt in patients during spinal anesthesia (Figures 2, 5, and 6). However, these cardiovascular responses to orthostatic tilt are attenuated in patients with congestive heart failure (23,24-26) or critical illness (28).

Therefore, some feasible causes of sudden cardiac arrest during spinal anesthesia could be attributed to severe derangement in the cardiopulmonary adjustments to changes in venous return induced by sympathetic blockade and/or body tilt. According to several previous reports (29-32), autonomic dysfunction has been claimed to be responsible for bradycardia and asystole in anesthetized and unanesthetized patients. Inasmuch as we cannot expect the onset of this severe derangement, it is only by continuous vigilance that catastrophic results can be avoided in clinical practice.

In summary, head-up body tilt during spinal anesthesia produces a significant HR increase in normal subjects without any cardiopulmonary disorders. This reflex HR increase is not impaired either by high level of spinal anesthesia or by sedation. The authors conclude that arterial baroreflex remains functional in the face of alterations in venous return associated with changes in body position even during high spinal anesthesia or mild sedation.

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Level of Spinal Anesthesia Can Be Predicted by the Cerebrospinal Fluid Pressure Difference Between Full-Flexed and Non-Full-Flexed Lateral Position

Seiji Watanabe, MD, PhD, Hiroshi Yamaguchi, MD, and Yumiko Ishizawa, MD

Department of Anesthesia, Mito Saiseikai General Hospital, Ibaraki, Japan

We studied whether cerebrospinal fluid pressure difference between full-flexed and non-full-flexed lateral position (dP) influences the spread of intrathecally (i.e., spinal) administered anesthetic solution (SSA). Forty-two women, 18–60 yr old, who underwent gynecologic surgery under spinal anesthesia were enrolled in the study. They were divided into two groups (group 1: <40 yr old, group 2: ≥40 yr old). Before spinal anesthetic injection, we measured the pressure difference produced by postural change from the right lateral decubitus position (non-full-flexed) for needle insertion at the L2-3 interspace to a full-flexed lateral decubitus position with a spinal needle in place. After they returned to the non-full-flexed lateral position, 14 mg of plain tetracaine in 10% dextrose solution (2.8 mL) was injected intrathecally in each patient. Pressure differences had a significant correlation with the cephalad levels of spinal anesthesia in each group; the larger pressure

difference was associated with a larger SSA. The relationship was stronger in the younger group (correlation coefficients, 0.82 and 0.63; *P*-values <0.01 in groups 1 and 2, respectively). Three patients in group 1 developed T-2 anesthesia, whereas no one in group 2 did (*P* < 0.01), and their pressure difference values ranged from 12 to 16 cm H₂O, substantially larger than those of the other patients in group 1. Five patients in group 2 developed T-3 anesthesia, whereas no patient in group 1 (*P* < 0.01) did, and their pressure differences were not essentially larger than those of the rest in the same group. The authors conclude that pressure differences correlated with the SSA, although the mechanism remains to be clarified. It seems possible to predict which patient in the younger patient group may develop unintentional high spinal anesthesia (T-3 or higher) by measuring pressure differences.

(Anesth Analg 1991;73:391–3)

Spread of intrathecally (i.e., spinal) administered anesthetic solution (SSA) is influenced by various factors, such as height, weight, anesthetic dose, baricity of spinal anesthetic solution, injection site, speed of injection, and posture (1,2). Provided these factors are similar, there is still interindividual difference in SSA in the subarachnoid space. Cerebrospinal fluid pressure (CSF-P) has been reported to be unrelated to SSA (2). The volume of CSF into which a local anesthetic solution is distributed is another determinant of SSA. Cerebrospinal fluid is contained in a single compartment, and its volume is kept constant during a brief increase of CSF-P (2) induced by full flexion, which increases intraabdominal pressure. Cerebrospinal fluid volume status may be assessed by CSF-P change produced by postural changes.

We, therefore, examined whether the CSF-P difference between full-flexed and non-full-flexed lateral position in individual patients influences SSA.

Methods

Forty-two female patients, without neurologic disease, hypertension, diabetes mellitus, large intraabdominal mass, or pregnancy, who underwent transabdominal hysterectomy or oophorectomy were studied. The study protocol was approved by the institutional review board. All patients were informed about the nature of the study and consent was obtained.

Patients were divided into two groups (group 1: 17 patients <40 yr old; group 2: 25 patients ≥40 yr old). All patients were premedicated with 1.0 mg of oral flunitrazepam 90 min before entering the operating room. Lactated Ringer's solution (500 mL) was infused before spinal anesthesia. In the right lateral decubitus position, a straight line was drawn between the C-7 and L-5 spinal processes and was set

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Address correspondence to Dr. Watanabe, Department of Anesthesia, Mito Saiseikai General Hospital, 3-3-10, Futabadai, Mito City, Ibaraki, 311-41, Japan.

horizontal using a water level adjuster and also by tilting the bed up or down as appropriate. A 23-gauge needle was inserted at the L2-3 interspace with the bevel toward the left side. After clear CSF appeared in the hub, a polyvinyl manometer catheter (1.5 mm in diameter, 50 cm in length, and 0.4 mL in volume) was connected to the hub and kept upright. When the flow of CSF stopped ascending the manometer, the height (in centimeters) from the level of the spinal tap (zero point) was read as CSF-P1. Next, CSF-P2 was measured when a patient tried to pull her chin down to the chest wall and draw her knees up onto the chest wall as much as possible with the aid of an assistant, but the patient was asked to keep her mouth open to avoid Valsalva maneuvers. After the tonometric measurements, the patient returned to non-full-flexed position and CSF-P3 was measured. To minimize further loss of CSF immediately after the manometer was disconnected, a spinal mixture of 2.8 mL of 10% glucose solution containing 14 mg of plain tetracaine was injected at the rate of 0.2 mL/s. The patient then returned to the supine horizontal position. The cephalad level of analgesia obtained 15 min after the injection was determined on the left mammary line by the pin-prick technique. Patients were excluded from the study if the difference between CSF-P1 and CSF-P3 was 2 cm H₂O or more.

We recorded the time needed for the tonometric procedure and the incidence of bloody taps and postdural puncture headache during the study. On the second or third postoperative day, we questioned the patients as to whether they had experienced headache or low back pain. The statistical analysis of the patients' data between groups 1 and 2 was performed using Student's *t*-test, and the difference between CSF-P1 and CSF-P2 values in each group was examined using paired Student's *t*-test. The correlation coefficients were calculated between height, weight, Broca index (weight \times 100/[height - 100]), age, CSF-P1, CSF-P2, pressure difference (CSF-P2 minus CSF-P1), and SSA (i.e., the number of spinal segments anesthetized above L-3) in each group. The number of patients who developed cephalad levels of T-2 and T-3 were compared between groups 1 and 2 using a χ^2 -test. *P*-values less than 0.05 were considered statistically significant.

Results

Two patients in group 1 and one patient in group 2 were excluded from the study because the difference between P1 and P2 was more than 2 cm H₂O. The mean values of height, weight, Broca index, CSF-P1, CSF-P2, pressure difference, and SSA were not significantly different between the groups. The mean value of CSF-P2 was larger than that of CSF-P1 in

Table 1. Patient Data

	Group 1	Group 2
Number	15	24
Age (yr)	31 \pm 7	47 \pm 5 ^a
Height (cm)	154 \pm 3	155 \pm 3
Weight (kg)	48 \pm 4	55 \pm 5
Broca index (%)	99 \pm 10	110 \pm 10
P1 (cm H ₂ O)	13 \pm 3	12 \pm 4
P2 (cm H ₂ O)	21 \pm 5 ^b	19 \pm 6 ^b
dP (cm H ₂ O)	8 \pm 4	6 \pm 4
SSA (segments)	10 \pm 2	10 \pm 2
Range	T6-2	T7-3

P1, cerebrospinal fluid pressure measured in the right lateral decubitus position; P2, cerebrospinal fluid pressure in the right lateral position with chin in chest and knees drawn up to chest; SSA, spread of spinal anesthetic solution; dP, pressure difference between P1 and P2.

Values are mean \pm SD.

^a*P* < 0.01 vs group 2.

^b*P* < 0.01 vs P1 in each group.

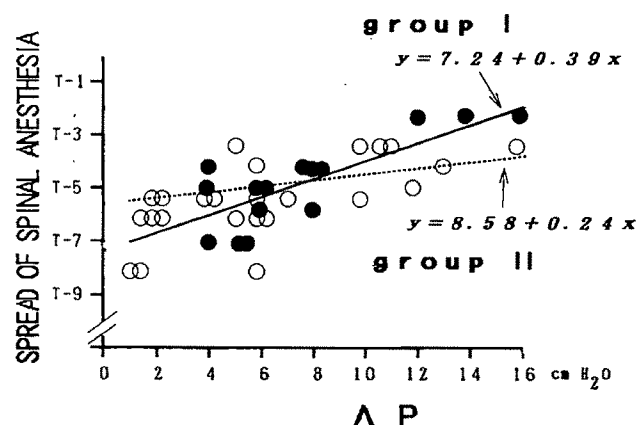


Figure 1. Cerebrospinal fluid pressure difference between flexed and nonflexed position (dP) and spread of spinal anesthesia (SSA). A larger dP value implies a larger spread, with more accuracy in group 1 (continuous line and filled circle) than in group 2 (dashed line and open circle). Note that in group 1 three patients with T-2 anesthesia had larger pressure differences than the others by more than 4 cm H₂O, whereas in group 2 five patients with T-3 anesthesia did not necessarily have larger pressure differences than the others. (Group 1: correlation coefficient = 0.82, *P* < 0.01; group 2: correlation coefficient = 0.63, *P* < 0.01.)

both groups, *P* < 0.01 (Table 1). In both groups, SSA had no significant correlation with height, weight, Broca index, CSF-P1, or CSF-P2, but there was a significant correlation between pressure differences and SSA in each group, *P* < 0.05 (Figure 1).

Three patients in group 1 developed anesthetic levels of T-2. Their pressure differences were 12, 14, and 16 cm H₂O, respectively, and these were larger than the pressure difference of any other patient by 4 cm H₂O or more (Figure 1). These three patients had no significant difference from the rest in the same group regarding height, weight, and Broca index. Five patients in group 2 developed T-2 anesthesia.

Their pressure differences ranged from 4 to 16 cm H₂O, which could distinguish these five patients from the rest in the same group (Figure 1). There were no significant differences between the five patients and the rest in group 2 regarding height, weight, and Broca index.

Bloody CSF was not observed during the study. The tonometric procedure per se was finished within about 1 min. There were no patients with postoperative back pain and/or postdural puncture headache in either group.

Discussion

Our results indicate that CSF-P1 did not have a significant correlation with SSA, as has been previously reported (2). Pressure difference is caused by epidural venous engorgement after increased intra-abdominal pressure and has a significant correlation with SSA.

The relationship between SSA and the volume of CSF in the lumbar and lower thoracic subarachnoid space has not been studied, but a recent editorial suggests that the lumbosacral CSF volume influences buffering capacity for local anesthetics and therefore SSA (3). We believe our results can be explained by the following logic. The larger pressure difference corresponds to the smaller CSF volume in the lumbar and lower thoracic subarachnoid space and to the larger SSA obtained. The larger pressure difference in the smaller CSF volume, however, seems to be contradictory to the presently accepted postulate (2). A patient with a smaller CSF volume may need a smaller spinal anesthetic dose than a patient of the same height with a larger CSF volume to achieve the same dermatome level of spinal anesthesia. A patient with a larger pressure difference is more comparable to a patient with a big abdominal mass sitting on the inferior vena cava than to those with a smaller pressure difference.

The three patients with T-2 anesthesia in group 1 had substantially larger pressure differences than the other patients in the same group. We can possibly prevent unintentionally high spinal anesthesia by measuring the pressure difference in younger individuals. However, because of the smaller correlation between SSA and pressure differences in group 2, the same postulate may not be as useful for older patients. In practical terms, prediction of high spinal anesthesia in the younger patient population may be more accurate than in the older population. The

present result may be partly due to the more flexible spine in the younger patients than in the older ones. The subclinical changes of aging are considered to begin at the age of 40 yr and are partly attributed to hormonal insufficiency (4). Regarding the influence of age on extent of anesthesia, our results are not necessarily in accordance with the previous reports suggesting poor predictability of the extent of anesthesia over a wide range of age (5,6).

The technical factors that may affect CSF dynamics in this study may be negligible because SSA is unaffected by a transient elevation of CSF-P (7). For fear of possible contamination, we did not return the CSF in the manometer after P3 measurement but the amount of the CSF lost was calculated to be about 0.1 mL. This was considered too small to influence SSA (8,9). Changing the patient's position with the spinal needle in place was not found to be hazardous. The approximate time of 1 min needed for tonometry seemed acceptable for both our patients and the operating room staff members.

In conclusion, we believe unintentional high spinal anesthesia is, to some extent, not only predictable by measuring the pressure difference but also preventable by tailoring the anesthetic dose according to it.

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Strength of Continuous Spinal Catheters

Stephen J. Ley, MD, and Brian R. Jones, MD

Department of Anesthesiology, School of Medicine, University of California, Davis, California

Several commercially available catheters are currently marketed for continuous intrathecal use. Initial studies using continuous spinal catheters have reported several occurrences of retained fragments after removal of the catheter. Accordingly, we measured the break strength of five commercially available catheters. The TFX/Rusch 28- and 32-gauge continuous spinal catheters required 3.18 and 1.92 lb to break, respectively. The Kendall 28-gauge, the Preferred Medical Products 24-gauge, and the 24-gauge Burron

catheters averaged 1.22, 1.97, and 3.55 lb to break, respectively. We also tested a commonly used Burron 20-gauge catheter, which is marketed for epidural use, and found it had an average break strength of 6.35 lb. The tested values obtained for the TFX/Rusch catheters were lower than the break strength values supplied by the manufacturers. The authors conclude that the break strength of spinal catheters is one-third to one-half that found for a typical epidural catheter.

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The development of small-diameter, continuous spinal catheters has renewed the popularity of continuous spinal anesthesia (1,2). Difficulties and complications of this technique still remain and include postdural puncture headache, inadequate anesthesia, paresthesias, risk of infection, and technical difficulties such as inability to thread the catheter, catheter kinking, and catheter breakage (3-5). A recent report highlighted these technical problems and presented catheter break-strength data (supplied by the manufacturers) for several continuous spinal catheters (6). Independent break-strength testing has not been reported. The strength of the catheter should be related to the possibility of breakage. Using the American Standard Testing Methods protocol (7), we tested the strength of five currently available continuous spinal catheters and present an independent analysis of catheter break-strength measurements.

Methods

Four new catheters of each type were purchased from each manufacturer: MicroSpinal 28- and 32-gauge (TFX/Rusch Inc., Duluth, Ga.), CoSpan 28-gauge (Kendall, Mansfield, Mass.), Preferred Medical 24-gauge (Preferred Medical Products, Richmond Hill, Ontario, Canada), and Burron 24-gauge (Burron

Medical, Bethlehem, Pa.) catheters. A Burron 20-gauge polyamide epidural catheter was also tested for comparison. All tests were performed at an independent materials testing laboratory (Matrecon Testing Labs, Alameda, Calif.).

The cross-section diameter of each specimen was measured with an electronic thickness gauge. The catheters were then cut into 20-cm segments, and double loops were tied at the end of each catheter segment. The distance between the knots was approximately 5 cm. Smooth metal rods were inserted through each loop and then into a constant rate of extension tensile testing machine (Instron Universal Testing Instrument, model 1130, Instron Corp., Canton, Mass.). The catheter segments were pulled 25 cm/min at $23 \pm 1^\circ\text{C}$. The American Standard Testing Methods protocols were followed for all tests (7). Four catheters of each type were tested in triplicate, providing 12 values. The results are presented as mean \pm standard deviation.

Results

All catheter segments broke at their midsection between the two knots, away from the loops where the force was applied. The average break strengths (in pounds) of the catheters were: Preferred Medical Products 24-gauge, 1.97 ± 0.22 ; Kendall 28-gauge nylon, 1.22 ± 0.14 ; TFX/Rusch 32-gauge, 1.92 ± 0.08 ; TFX/Rusch 28-gauge, 3.18 ± 0.16 ; Burron 24-gauge, 3.55 ± 0.21 ; Burron 20-gauge epidural, 6.35 ± 0.35 . (For further details, see Table 1.)

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Address correspondence to Dr. Jones, Department of Anesthesiology, School of Medicine, TB-170, Davis, CA 95616.

Table 1. Break Strength

Manufacturer	Gauge	Outside diameter (mm)	Break strength (lb)	
			Present tests ^a	Advertised
TFX/Rusch Medical	32	0.233	0.93 ± 0.13 ^b	
			1.92 ± 0.08 ^c	2.6
TFX/Rusch Medical	28	0.370	1.57 ± 0.28 ^b	
			3.18 ± 0.16 ^c	4.2
Kendall	28	0.355	1.22 ± 0.14	<i>d</i>
Preferred Medical	24	0.566	1.97 ± 0.22	<i>d</i>
Burrton	24	0.542	3.55 ± 0.21	<i>d</i>
Burrton (epidural)	20	0.858	6.35 ± 0.35	7.0 ^e

^aMean ± SD.^bCatheter.^cStainless steel stylet.^dNot included in manufacturer's report.^ePersonal communication from Burrton Medical.

The values reported for the TFX/Rusch catheters are the force required to break the stainless steel stylet. The polyamide tubing that surrounds and is adherent to the stylet broke after the stylet broke. The catheter alone required greater elongation to break and had lower break strengths than the stylet: 0.93 ± 0.13 and 1.57 ± 0.27 lb for the 32- and 28-gauge catheters, respectively.

Discussion

It is important to discriminate between tensile strength and break strength. Tensile strength is expressed in pounds per square inch and is consequently difficult to measure when the cross-sectional area is difficult to measure such as in catheters with hollow lumens. By convention, round extruded materials are evaluated by break strength. Break-strength testing is usually done with the test material clamped at each end. We used a modified method with smooth rods in place of clamps. When clamps were used, the pressure from the clamps weakened the material and caused a premature break.

To approximate what a clinician might do if a catheter is difficult to remove, the catheters were pulled at 25 cm/min. The pull speed used during previously reported break-strength testing was not reported (6). When polymers are pulled very slowly, the material flows and partial crystallization occurs. In this situation, more force may be required to break a sample. It is possible that a slower pull speed would yield a larger break-strength value than what we ob-

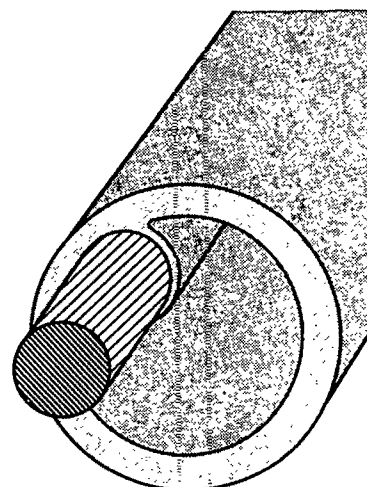


Figure 1. The TFX/Rusch catheter has a metal stylet permanently imbedded into the side wall. The built-in stylet remains in place to improve the break strength of the catheter.

tained; however, a pull speed slower than 25 cm/min may not be clinically relevant.

In this study, the break-strength values for the TFX/Rusch 32- and 28-gauge catheters were lower than those reported by the manufacturers. The Preferred Medical's manufacturing process has been modified, and recently, manufactured catheters may have greater strength than the catheters we tested. Preferred Medical also manufactures 28- and 32-gauge polyurethane catheters marketed for continuous spinal use, but they were not available to us when we did our testing.

The TFX/Rusch catheters are unique in that they are a combination of two materials. The metal stylet is permanently fused to the flexible catheter material (Figure 1). The metal stylet provides the majority of the strength. There is the concern that the stylet could kink and weaken (or even break) and the catheter could still appear intact.

In summary, break strengths for three continuous spinal catheters are approximately one-third to one-half the break strength of a commonly available epidural catheter. The break-strength values we obtained were also different from those previously reported. Break-strength testing should continue to be a vital part of manufacturing quality control, and extreme caution should be used when these catheters are removed.

We thank Dr. Henry Haxo and Matrecon Testing Labs for their help and guidance during this project.

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Comparison of 40 Milliliters of 0.25% Intrapleural Bupivacaine With Epinephrine With 20 Milliliters of 0.5% Intrapleural Bupivacaine With Epinephrine After Cholecystectomy

Kjell E. Strömskag, MD, PhD, Bruce G. Minor, DrMedSc, and Anders Lindeberg, MSc
Department of Anesthesiology, Molde County Hospital, Norway; Astra Pain Control AB, Södertälje, Sweden

To determine the influence of the volume of local anesthetic injected for intrapleural analgesia, 40 patients undergoing cholecystectomy were randomly allocated to two groups of 20 patients each. One group received 40 mL of 0.25% bupivacaine with epinephrine injected intrapleurally postoperatively. The other group received 20 mL of 0.5% bupivacaine with epinephrine. The onset time of analgesia was nearly the same in both groups and within 25 min all

patients were nearly pain free. Our data demonstrate that 100 mg of bupivacaine with epinephrine elicits effective analgesia after cholecystectomy. There are only minor differences between 20 and 40 mL with regard to pain relief. The authors conclude that the volume of local anesthetic within the range of 20–40 mL in an adult has little influence on the extent or duration of intrapleural analgesia.

(Anesth Analg 1991;73:397–400)

Surgery and postoperative pain adversely affect ambulation and respiratory function. After upper abdominal surgery the incidence of pulmonary complications increases due to difficulty in coughing and taking deep breaths (1). Traditional use of postoperative narcotic analgesics is associated with side effects, especially respiratory depression (2). Intrapleural administration of local anesthetics has been reported to relieve pain after upper abdominal surgery (3–5). Many authors recommend 20 mL of 0.5% bupivacaine for intrapleural injection, but 20 mL of 0.25% bupivacaine is also satisfactory for pain relief (4). The effect of larger volumes of the local anesthetic solution on intrapleural analgesia is unknown.

The objective of this study was to determine whether the volume of local anesthetic injected intrapleurally influences the effectiveness and duration of postoperative analgesia after upper abdominal surgery.

Methods

This investigation was approved by the local ethical committee and was performed in accordance with the

recommendations of the Helsinki Declaration. Informed consent was obtained from each patient. Patients with a history of pneumothorax, hemothorax, severe heart failure, or allergy to local anesthetics were excluded.

Forty patients who had undergone cholecystectomy (subcostal incision) were included in this blinded study. They were randomized into two groups to be given either 20 mL of 0.5% bupivacaine with epinephrine (5 μ g/mL) or 40 mL of 0.25% bupivacaine with epinephrine (5 μ g/mL). Oxazepam (25–75 mg) was given orally 1–2 h before induction of anesthesia. Surgery was performed under general anesthesia with thiopental, fentanyl (mean 0.6 ± 0.2 mg)/alfentanil (mean 4 ± 1 mg), pancuronium/vecuronium, and nitrous oxide/oxygen.

After completion of surgery but before extubation of the trachea, the patients were turned to the left side, and an epidural catheter (Portex 16-gauge, closed end with three lateral eyes) was introduced 5–6 cm into the right pleural space through a 16-gauge Tuohy needle inserted at the eighth or ninth intercostal space, just above the upper edge of the lower rib, 8–10 cm from the midline posteriorly (3,4). General anesthesia was then discontinued.

When the patient reported pain after surgery, either 20 or 40 mL of the bupivacaine solution was injected intrapleurally in a randomized manner. The

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Address correspondence to Dr. Strömskag, Department of Anesthesia, Molde County Hospital, N-6400 Molde, Norway.

Table 1. Demographic Data of the Patients Studied

	Age (yr)	Weight (kg)	Height (cm)	Duration of operation (min)	Time of operation (min)	Sex Male/female
40 mL of 0.25% bupivacaine	64 ± 16	71 ± 16	165 ± 6	131 ± 54	200 ± 83	5/15
20 mL of 0.5% bupivacaine	60 ± 13	69 ± 8	169 ± 6	142 ± 69	194 ± 70	6/14

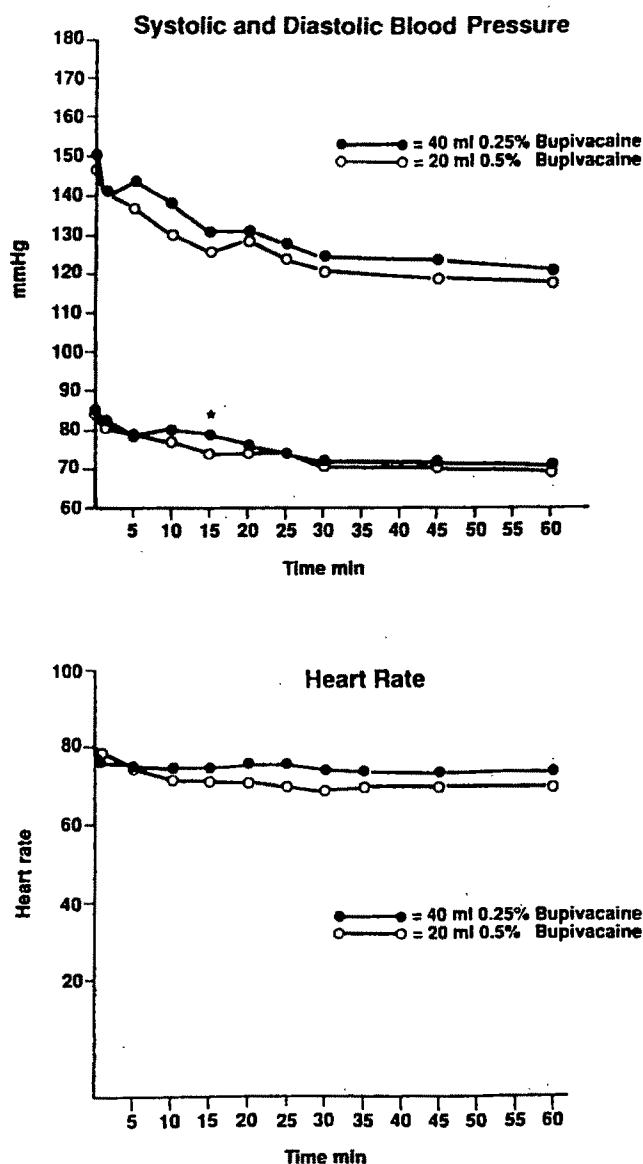


Figure 1. Heart rate and systolic and diastolic arterial blood pressures before and for 60 min after intrapleural injection of 20 mL of 0.5% bupivacaine with epinephrine or 40 mL of 0.25% bupivacaine with epinephrine. * $P < 0.05$.

person who conducted the examination and scoring postoperatively was unaware of the volume of the bupivacaine solution that had been injected. Injection took approximately 60 s with 5 mL being first injected as a test dose. The degree of postoperative pain using

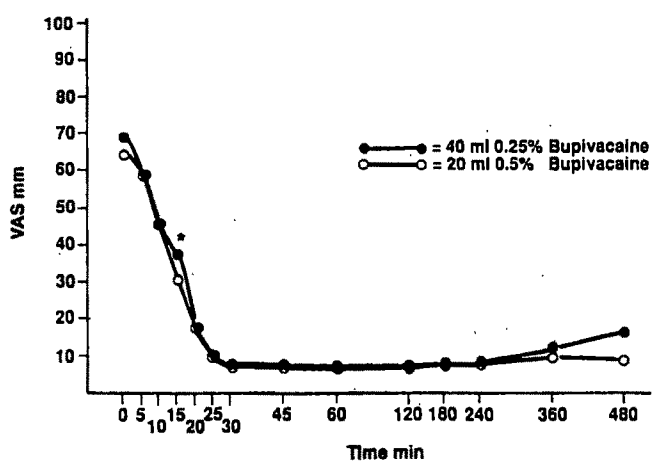


Figure 2. Pain (VAS) after intrapleural injection of 20 mL of 0.5% bupivacaine with epinephrine or 40 mL of 0.25% bupivacaine with epinephrine. * $P < 0.05$.

a visual analogue scale (VAS, 0–100 mm) was assessed when the patient first complained of pain after surgery and 2, 5, 10, 15, 20, 25, 30, and 45 min and 1, 2, 3, 4, 6, and 8 h after intrapleural injection. Use of supplementary analgesics was recorded.

The extent of the sensory anesthesia was determined by pinprick at the same time that the level of pain was recorded. The duration of the analgesia was regarded as the period starting when the patient became free of pain to the time when further analgesics were required.

Systolic and diastolic arterial blood pressures and heart rate were recorded before injection and 2, 5, 10, 15, 20, 25, 30, and 45 min and 1, 2, 3, 4, 6, and 8 h after intrapleural injection. Side effects and complications were recorded. Postoperative chest radiographs were taken after 24 h. Visual analogue scale data were evaluated for statistical significance by repeated measures analysis. For the purpose of statistical analysis, a Wilcoxon signed rank test, Fisher two-sided test, χ^2 test, and analysis of variance t -test were used. A P value of 0.05 indicated statistical significance. The results are expressed as medians.

Results

Data on age, patient weight, height, sex, duration of operation, and times between operation and injection

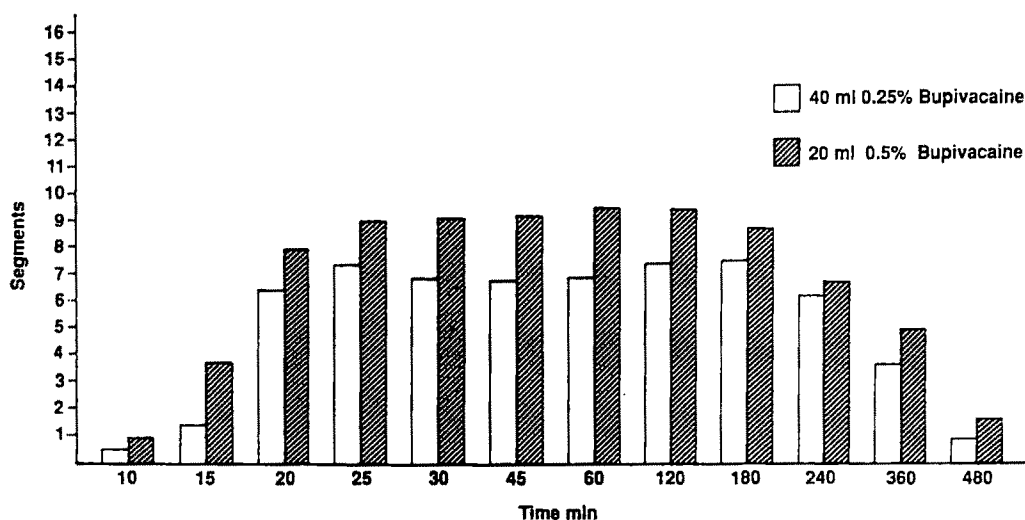


Figure 3. Number of segments of sensory analgesia after intrapleural injection of 20 mL of 0.5% bupivacaine with epinephrine or 40 mL of 0.25% bupivacaine with epinephrine.

(Table 1) showed no significant differences between the groups.

Heart rate and systolic and diastolic arterial blood pressures are shown in Figure 1. Differences in arterial blood pressure and heart rate were not significant except at 15 min.

The pain scores on a VAS scale are shown in Figure 2. Nearly complete pain relief was obtained within 25 min in both groups. After 15 min the VAS levels were lower in patients given 20 mL of 0.5% bupivacaine than in patients who received 40 mL of 0.25% bupivacaine (30.0 vs 37.7 mm; Figure 2).

The median duration of analgesia in the group given 20 mL of 0.5% bupivacaine was 435.0 min. In the group given 40 mL of 0.25% bupivacaine, the median duration was 437.5 min. The difference was not statistically significant.

Differences in sensory anesthesia were not statistically significant in the two groups (Figure 3). In the group given 20 mL of 0.5% bupivacaine, a median of 10.5 segments was recorded at the time of maximal spread. In the group given 40 mL of 0.25% bupivacaine, the median was 8.6 segments. Time for maximal spread was the same in both groups (30 min). Chest radiographs on the first postoperative day were negative for pneumothoraces in all patients.

Discussion

The intrapleural analgesic technique has been used for management of postoperative pain after unilateral surgery in the upper abdomen (3-7). The effectiveness of this method after thoracotomies is more variable and may even be ineffective (8), perhaps because a major portion of the local anesthetic drug

was lost by suction through a chest tube. Intrapleural regional anesthesia has also been used for multiple rib fractures, herpes zoster, thoracic and pancreatic pain, and sympathetic reflex dystrophy (9-13). There are still, however, questions as regards the optimal volumes of local anesthetic solutions for intrapleural injection. From 2 to 30 mL have been injected with good effect (10-14). Another report indicates that 30 mL of 0.5% bupivacaine was needed to elicit an effective blockade (8). Thirty milliliters of 0.75% bupivacaine with or without epinephrine (maximum plasma concentration, 2.50 $\mu\text{g/mL}$) elicited no side effects, and the frequency of administration of narcotics decreased and the hospital stay decreased (15). In other studies, this dosage (30 mL of 0.75% and 30 mL of 0.5% bupivacaine) was found to elicit high plasma concentrations (4.9 $\mu\text{g/mL}$) (14,16).

Our study shows that the volume makes little difference with regard to effectiveness of intrapleural injection in relieving postoperative pain. The onset time is the same with injection of either 40 mL of 0.25% or 20 mL of 0.5% bupivacaine. After 15 min there was a statistically significant difference on VAS with 37.7 mm after injection of 40 mL of 0.25% bupivacaine and 30.0 mm after injection of 20 mL of 0.5% bupivacaine.

We conclude that the volume of local anesthetics within the range of 20-40 mL, with the same dosage, has little effect with respect to extent and duration of analgesia after intrapleural injection of bupivacaine with epinephrine.

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Onset of Epidural Blockade After Plain or Alkalinized 0.5% Bupivacaine

Christian Verborgh, MD, Marie-Anne Claeys, MD, and Frederic Camu, MD

Department of Anaesthesiology, Flemish Free University of Brussels, Brussels, Belgium

This double-blind study investigated the effect of adding 1.4% bicarbonate to 0.5% bupivacaine on onset time of sensory and motor blockade after epidural administration. Forty patients were randomly divided into one of two groups. Group 1 received 20 mL of 0.5% bupivacaine (pH, 5.58 ± 0.12) and group 2 received 20 mL of 0.5% bupivacaine + 0.6 mL of 1.4% bicarbonate (pH, 6.53 ± 0.06). Onset of temperature sensation loss occurred at L-1 after 5 min in both groups. The first signs of motor impairment

were seen after 4 min in three patients in group 1 and two patients in group 2. Maximum motor blockade was reached after 30 min in group 1 and after 36 min in group 2. No difference in motor blockade or upward spread of anesthesia was noted between the two groups. The authors conclude that alkalinization of 0.5% bupivacaine offers no improvement in the onset of epidural blockade.

(Anesth Analg 1991;73:401-4)

There is considerable disagreement as to whether alkalinization of 0.5% bupivacaine hastens the onset of epidural blockade. Benhamou et al. (1) and Stevens et al. (2,3) reported no difference in the time required to reach a certain dermatome, or difference in spread, whereas Mc Morland et al. (4) and Tackley and Coe (5) documented faster onset of sensory blockade. In these papers either pregnancy (1,4,5) or the addition of epinephrine (1-3,5) may have influenced the results reported. Indeed, the addition of epinephrine to a local anesthetic shortens the onset of epidural blockade (6) and pregnancy alters the onset and spread of epidural blockade, possibly by various mechanisms (7-9). We therefore tested the hypothesis that alkalinization of 0.5% bupivacaine without epinephrine increases the speed of onset of sensory and motor blockade after epidural administration in non-pregnant patients in a randomized, double-blind study.

Methods

Forty patients (ASA physical status I) scheduled for orthopedic surgery gave informed consent for participating in the study. The study protocol was approved by the hospital ethics committee. The demographic data of the patients are shown in Table 1. The

patients were given 0.5 mg of atropine 30 min before the start of the procedure. Upon arrival in the recovery ward, 750 mL of crystalloid was given intravenously. The patients were then placed in a seated position. After local skin infiltration at the L4-5 intervertebral space with 3 mL of 2% lidocaine, a 17-gauge Tuohy needle was inserted and advanced until the epidural space was identified. The patients were divided according to a randomized protocol into two groups to receive plain or alkalinized bupivacaine solutions prepared by a second anesthesiologist, so that the evaluating anesthesiologist could remain unaware of the nature of the solution. The patients in group 1 received 20 mL of a solution consisting of 40 mL of 0.5% bupivacaine. The patients in group 2 received 20 mL of a solution consisting of 40 mL of 0.5% bupivacaine to which 1.2 mL of 1.4% sodium bicarbonate had been added. After injection, the glass tray with the remaining 20 mL was handed over to the first anesthesiologist who made the pH evaluations. pH was measured on-line using a Novolog pH meter with a glass electrode and an error reading of 0.01. The end of the injection was considered as point 0 of the time measurements. Evaluation of loss of temperature sensation was performed using an ice cube every 2 min for 40 min. Motor blockade was evaluated at 2-min intervals at three different joints (hip, knee, and foot), with a three-grade response to extension (2 for no impaired movement, 1 for partial movement, 0 for no movement), providing a total score of 12 for a bilateral evaluation. Randomization

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Address correspondence to Dr. Verborgh, Academisch Ziekenhuis V.U.B., Department of Anaesthesiology, Laarbeeklaan 101, B-1090 Brussels, Belgium.

Table 1. Demographic Data on Patients

	Group 1	Group 2
Age (yr)	37 ± 3	35 ± 3
Weight (kg)	70 ± 2	68 ± 2
Height (cm)	170 ± 2	169 ± 2
M/F	14/6	12/8

All values are mean ± SEM.

was performed using randomization tables (Geigy scientific tables). Times until loss of temperature sensation and motor blockade scores were treated for descriptive statistics. Values are expressed as mean ± SEM with the exception of scores, which are expressed as medians. Kruskal-Wallis one-way analysis of variance and Wilcoxon signed rank test were used for comparison within groups. Friedman two-way analysis of variance and Mann-Whitney U-test were used for comparisons between groups. These tests were performed using STATGRAPHICS v.4.0 (STSC, Inc). $P < 0.05$ was considered significant.

Results

The two groups were comparable with respect to age, weight, and height (Table 1). pH measured at the time of injection was 5.58 ± 0.12 in group 1 and 6.53 ± 0.06 in group 2. No precipitation was visible at that time. However, during the 40-min observation period, the observed pH values increased slowly to 5.70 ± 0.06 in group 1. In a similar way the pH readings in group 2 increased significantly to 7.04 ± 0.04 . Precipitation was observed after 40 min in all samples in group 2, even though in some, pH was lower than 7.0. Comparison of pH between the two groups was highly significant.

The first dermatome to lose temperature sensation was L-1 after 5 min in both groups (Figure 1). S-1 took 22 min in group 1 and 21 min in group 2. L-5 took 16 and 15 min, respectively. There were no significant differences between the two groups with respect to time until temperature sensation loss for the dermatomes evaluated. Upward spread was not statistically different in the two groups (Figure 2).

The first signs of motor impairment were discernable after 4 min in three patients in group 1 and two patients in group 2 (Figure 3). The lowest median score, which was 4 in both groups, was reached after 30 min in group 1 and 36 min in group 2. Lowest upper-quartile was 6 in group 1 and 8 in group 2 and was reached after 28 and 18 min, respectively. Lowest lower-quartile was 4 in both groups and was reached after 22 min in group 1 and 26 min in group 2. A maximum interquartile range of 4 was observed after 8, 10, 14, 22, and 24 min in group 1 and after 8, 26, 28,

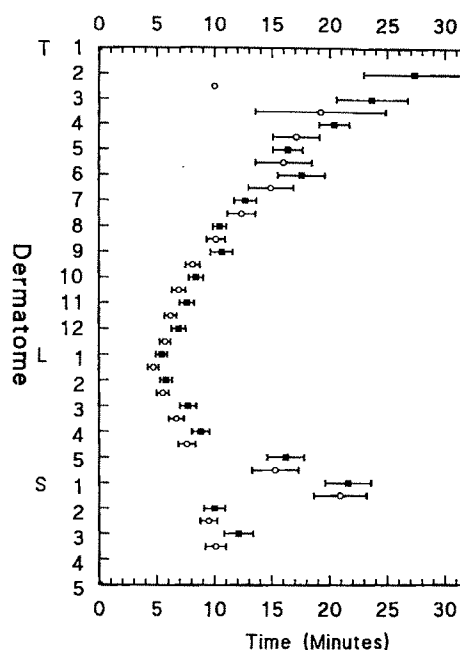


Figure 1. Mean time ± SEM until start of temperature sensation loss for the different dermatomes after epidural administration of plain 0.5% bupivacaine (group 1, —■—) or alkalized 0.5% bupivacaine (group 2, —○—).

30, 32, 34, 36, 38, and 40 min in group 2. However, motor blockade was not significantly different between the two groups.

Discussion

In our study the addition of 1.4% bicarbonate to 0.5% bupivacaine did not alter onset, spread, or degree of motor blockade after epidural administration. These findings are in agreement with two other reports (1,2). Benhamou et al. (1) did not find any difference in onset of sensory blockade or time to reach the maximum level of anesthesia after epidural administration of alkalized or plain 0.5% bupivacaine in pregnant patients. It was shown in one animal study that pregnancy shortens onset time of nerve blockade after bupivacaine (7). It is not known whether this effect should be attributed to the effect of hormonal factors on the membrane (9) or to enhanced diffusion (7). The effect of alkalization in this study could have been clouded by an already enhanced diffusion caused by pregnancy. Stevens et al. (2) used a safety pin to determine onset of analgesia at L-2 and found no difference after epidural administration of plain or alkalized 0.5% bupivacaine with epinephrine (1:200,000). Because of its pharmacologic interference during a nerve block, we choose to omit epinephrine in our study. Although the time between preparation of the solutions and their administration was not

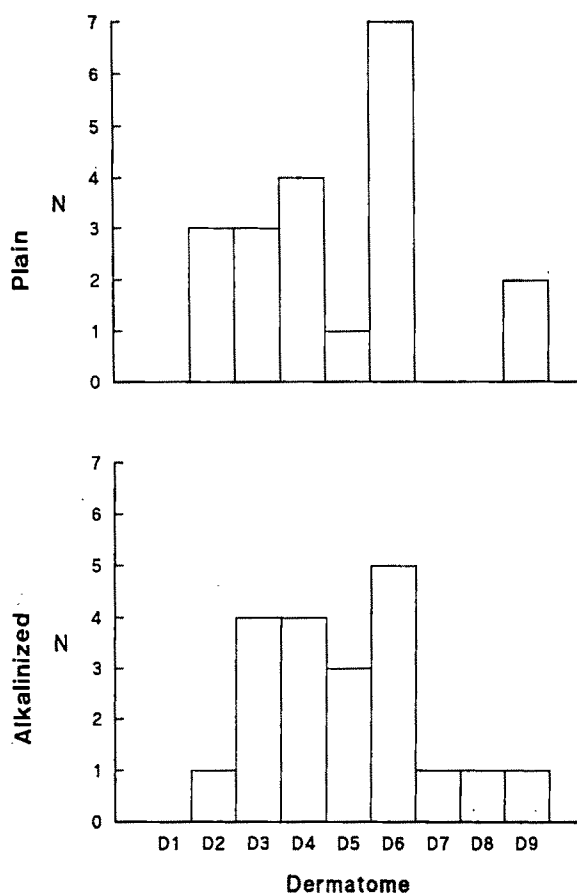


Figure 2. Frequency histogram showing upper level of temperature sensation loss reached 40 min after epidural administration of plain (group 1: top) or alkalized (group 2: bottom) 0.5% bupivacaine.

mentioned in those reports, we took the utmost care in minimizing this interval. Indeed, a previous report (10) established the importance of reducing this time to a minimum. By exposing the solution to surrounding air, CO₂ escapes at the air-solution interface, thereby increasing pH and causing more precipitation of bupivacaine base, which was clinically observed in the remainder of our alkalized solutions after the observation period. Although a laboratory report by Bonhomme et al. (11) demonstrated the stability of concentration after 6 h in the presence of precipitation, we believe that the homogeneity of the solution is lost, which may lead to errors in dosing especially if only part of the solution is injected and crystalloid precipitation is left in the recipient.

As prewarming of the solution to 37°C (12,13) could have a separate effect on increasing the speed of onset, the solutions were prepared at room temperature to document more clearly any potential difference in the speed of onset. Furthermore, the presence of more nonionized amide is favored by increasing temperature due to lowering the pK_a (14),

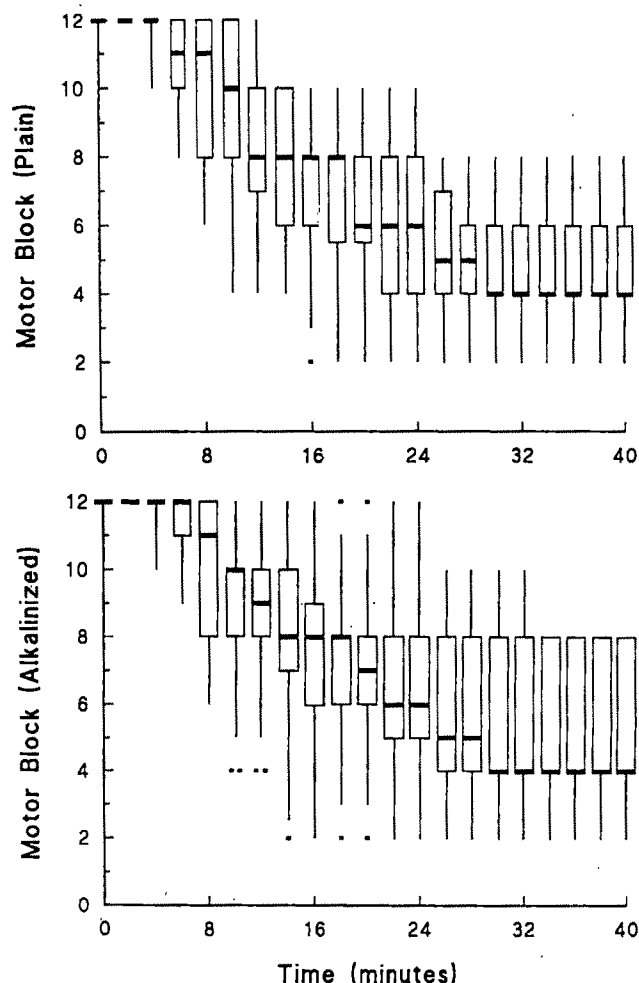


Figure 3. Box and whisker plot of degree of motor blockade at different times after epidural administration of plain (group 1: top) or alkalized (group 2: bottom) 0.5% bupivacaine. The central box covers the middle 50% of the motor blockade scores between the lower and the upper quartiles. The whiskers extend out to the extremes (minimum and maximum scores), and the central bar is at the median. Observed scores that exceed 1.5 times the interquartile range are drawn separately.

making a comparison with other studies or clinical circumstances more difficult. A modification of degree of crystallization caused by warming, as mentioned recently (15,16), would not have been relevant because of the rapid administration of our solutions.

Two authors did find a difference in onset of epidural blockade due to alkalization of bupivacaine in pregnant patients. Mc Morland (4) used 0.25% bupivacaine in smaller doses to determine onset at T-12-L-1. The failure of detection of any difference in our group may have been caused by an overshoot in concentration. Independent of the theoretical consideration that a larger concentration in situ hastens perineural diffusion and thus the effect (17), concentration may have been too high, provoking massive perineural transfer irrespective of pH.

Such a transfer may have been more than necessary to be effective, thereby obviating any difference caused by alkalization. Tackley and Coe (5) added epinephrine in the alkalized group and the faster onset in this group might be an effect of the epinephrine as well as the alkalization.

A possible shortcoming of this study is the lack of information on CO₂ tension in solution (18). Preliminary efforts to determine CO₂ tension failed to provide an end-point measurement. This is probably due to constant reequilibration of CO₂ between the aqueous and air phase while working on an open recipient, a problem that is not encountered in closed vials.

The alkalization of bupivacaine seems to produce more parallel study conclusions for different block procedures. No benefit was demonstrated for onset time in different spinal block studies (19-21) after alkalization of a 0.5% bupivacaine solution with or without epinephrine. In brachial plexus block (22), onset time was also not different between the alkalized and plain groups. On the contrary, a clear difference in onset of akinesia (23,24) was demonstrated in peribulbar block with plain or alkalized 0.75% bupivacaine with hyaluronidase, which by itself may display a different activity in alkaline medium. This study did not demonstrate any difference between alkalized and plain 0.5% bupivacaine for onset of sensory and motor blockade. We conclude that there is no benefit from the addition of bicarbonate to bupivacaine for epidural blockade.

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Epidural Sufentanil for Postoperative Analgesia: Dose-Response in Patients Recovering From Major Gynecologic Surgery

George Graf, MD, Raymond Sinatra, MD, PhD, James Chung, MD, Anthony Frasca, MD, and David G. Silverman, MD

Department of Anesthesiology, U.C.L.A. School of Medicine, Los Angeles, California; Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

To determine the lowest effective dose of epidural sufentanil given for analgesia, 41 patients undergoing elective abdominal gynecologic surgery during continuous epidural anesthesia (lidocaine 2%) were randomly assigned to one of four postoperative treatment groups. Patients received an epidural bolus of either 25 (group A), 40 (group B), 55 (group C), or 70 μ g (group D) sufentanil in 10 mL of saline. They were evaluated for the next 8 h using a 10-cm visual analogue scale. Except for two individuals in group A, all patients achieved a visual analogue scale score of 1 cm or less during the study interval. The onset of analgesia was most rapid in the two higher dose groups (A vs C and D; $P < 0.05$). Pairwise comparison between groups showed a significant difference in the time needed to achieve maximum pain relief

between the lowest and highest treatment groups (A vs D; $P < 0.05$). Duration of analgesia was also significantly longer in groups C and D than in group A (208.0 ± 21.1 and 224.0 ± 14.7 vs 140.0 ± 10.7 min; $P < 0.05$). There were no differences among groups with regard to mean respiratory rate, level of sedation, 24-h narcotic requirements, or incidence of nausea, vomiting, and pruritus ($P = \text{NS}$). A single patient in group D suffered profound respiratory depression within seconds of administration. We conclude that, in patients recovering from lower abdominal surgery, a single 40–55- μ g epidural bolus of sufentanil provides 3–3.5 h of effective analgesia, and that larger doses are not warranted.

(Anesth Analg 1991;73:405–9)

Epidural administration of sufentanil provides highly effective analgesia after general surgery (1–3) and cesarean section (4,5). The drug's high lipid solubility and μ -receptor affinity (6) promote the rapid onset of intense analgesia (1–3). Alternatively, sufentanil's relatively short duration (1,2), high epidural dose requirement (3–5), and potential for acute-onset respiratory depression (7,8) may limit its overall usefulness in this setting. Perhaps epidural sufentanil would be an effective initial analgesic, providing a period of profound analgesia during which additional means of pain control could be initiated. The present prospective randomized

dose-response study sought to determine the lowest effective dose(s) of epidural sufentanil that could provide analgesia of rapid onset in patients experiencing pain after lower abdominal surgery.

Methods

The study was approved by the Human Investigations Committee of Yale University School of Medicine, and informed consent was obtained from all patients preoperatively. Forty-one ($n = 41$) ASA physical status I or II patients undergoing elective abdominal gynecologic surgery with continuous epidural anesthesia were randomly assigned to one of four patient treatment groups. Pregnancy, a history of drug abuse, major organ disease, age less than 18 yr or greater than 65 yr, or weight less than 40 kg or greater than 110 kg were criteria for exclusion from the study.

Patients were premedicated with 0.03–0.04 mg/kg IM midazolam. Anesthesia was provided via a lumbar epidural catheter (L2–3, L3–4) using 2% lidocaine

This study was performed in its entirety at the Yale-New Haven Hospital, Yale University School of Medicine.

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Address correspondence to Dr. Graf, Department of Anesthesiology, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, Room 8211, Los Angeles, CA 90048.

with epinephrine (1:200,000). A sensory level of T1-4 was achieved before the commencement of surgery. Intravenous benzodiazepine (0.02–0.04 mg/kg midazolam) was used for intraoperative sedation, and small doses of intravenous fentanyl (25–100 μ g total dose) were used to blunt discomfort associated with upper abdominal exploration. Such medication was withheld within 30 min of the end of the surgery.

At the conclusion of surgery, patients were transferred to the postanesthesia care unit, where they were monitored by the staff and a research nurse observer specifically assigned to the patient. When analgesia was first requested, patients were given a single bolus of either 25 (group A), 40 (group B), 55 (group C), or 70 μ g (group D) of sufentanil via the epidural catheter over a 1-min period by a physician investigator. All study drugs were prepared and coded in advance by an investigational pharmacist and diluted in normal saline to a volume of 10 mL.

Pain intensity, vital signs, and level of sedation were assessed at the following times: before the administration of the study drug (baseline); at 5, 10, 15, 30, 45, and 60 min after injection; at subsequent 30-min intervals until additional pain medication was requested; and then at hourly intervals for the remainder of the 8-h study period. All patients received either intramuscular morphine sulfate or meperidine hydrochloride. Pain intensity was assessed using a visual analogue scale (10 cm VAS), anchored with "no pain" at 0 and "worst pain imaginable" at 10. The following variables were determined:

1. The onset of analgesia defined as the time in minutes from injection of the study medication to the first reduction in pain intensity (VAS) of at least 1 cm on two consecutive evaluations.
2. The time from study drug administration until a 50% reduction from baseline VAS was achieved ($T = 50\%$).
3. Time to the lowest VAS score (VAS_{min}).
4. Lowest VAS score (VAS_{min}).
5. MAXPID: the maximum pain intensity difference (VAS) from baseline over the 8-h observation period.
6. The duration of analgesia defined as the time between onset of analgesia and either a return to baseline VAS or the time when additional pain medication was required (whichever occurred first).
7. VAS pain scores when the patient received the study medication ($VAS_{baseline}$) and VAS scores when the patient requested additional medication (VAS_{end}).

The level of sedation was assessed using the following scale: 0 = alert; 1 = drowsy, oriented; 2 = drowsy, disoriented; 3 = very drowsy, disoriented.

Respiratory rate was continuously assessed by an apnea monitor (Air Shields); and side effects including nausea, vomiting, pruritus, and respiratory depression (respiratory rate < 10 breaths/min) were documented and treated as required.

The amounts of intramuscular morphine and meperidine administered to the patient during the first 24 h after the first request for additional pain medication were tabulated. Drug dosages were recorded in morphine equivalents (10 mg IM meperidine = 1 mg IM morphine) to facilitate comparison.

Data are reported as mean \pm SD. Demographic variables and side effects within the four treatment groups were compared simultaneously via analysis of variance for continuous variables or the χ^2 -test for categorical variables. For baseline pain intensity, the four treatment groups were compared via one-way analysis of variance. For each computed parameter, the data were analyzed by analysis of covariance with baseline VAS as the covariate. Subsequently, pairwise comparisons of the four treatment groups were carried out via individual *t*-tests on the least-squares (adjusted) means. Statistical tests with *P*-values of 0.05 or less were considered significant. Based on the objectives of the study, there were only a small number of key pairwise comparisons. Thus, a Bonferroni correction of *P*-values was not applied.

Results

The four treatment groups were similar with respect to age, weight, height, and ASA physical status (Table 1). All patients were female ranging in age from 25 to 61 yr (mean 41 ± 7) and in weight from 44.6 to 102.2 kg (mean 65.3 ± 12.2). All patients underwent gynecologic procedures and received horizontal lower abdominal incisions. There were no significant differences among the groups with regard to the amount of intraoperative midazolam or fentanyl administered, level of sedation, extent of residual sensory blockade at the time analgesia was requested, or $VAS_{baseline}$. There was no difference between groups with regard to the incidence of adverse effects (Table 2). All patients in groups B (40 μ g), C (55 μ g), and D (70 μ g) achieved an excellent level of analgesia with VAS_{min} of 1 cm or less. Two individuals in group A did not report a VAS below 1 cm (Table 3).

All four treatment groups exhibited a dose-response with respect to onset (Table 2). Treatment group A (25 μ g) had an onset of analgesia significantly longer than either group C (55 μ g) or group D (70 μ g). A dose effect was also noted for time to the lowest VAS score (VAS_{min}), with group D achieving maximum analgesia sooner than group A ($P < 0.05$).

The four sufentanil groups also displayed a dose-

Table 1. Patient Characteristics by Group

Group	Sufentanil bolus (μ g)	Age (yr)	Weight (kg)	Height (in)	Time to drug administration ^a (min)
A	25	42.2 \pm 6.32	64.6 \pm 7.97	64.3 \pm 2.14	67 \pm 26
B	40	36.7 \pm 6.48	62.0 \pm 7.68	64.1 \pm 2.13	69 \pm 23
C	55	42.4 \pm 7.85	67.1 \pm 15.66	63.1 \pm 1.61	80 \pm 39
D	70	42.8 \pm 6.52	68.2 \pm 16.01	64.4 \pm 2.60	81 \pm 33
	P	NS	NS	NS	NS

NS, not significant.

Values are mean \pm SD.^aTime from end of surgery until epidural administration of study drug.**Table 2.** Summary of Effectiveness: Time-Course

Parameter	Group A (25 μ g)	Group B (40 μ g)	Group C (55 μ g)	Group D (70 μ g)
Onset time ^a (min)	18.0 \pm 12.0 ^b	12.0 \pm 12.0	06 \pm 06	06 \pm 06
Time to 50% reduction from baseline (min)	18.0 \pm 12.0	18.0 \pm 12.0	12.0 \pm 6.0	12.0 \pm 6.0
Time to lowest VAS _{min} (min)	49.7 \pm 29.4 ^c	35.5 \pm 19.0	38.1 \pm 27.9	24.8 \pm 18.3
Duration of analgesia (min)	140 \pm 10.7 ^d	161.5 \pm 18.5	208 \pm 21.1	224 \pm 14.7

Values are mean \pm SD.^aOnset, time from injection to first reduction in pain intensity of at least 1 cm in two consecutive evaluations.^bSignificant difference between group A and groups C and D, $P < 0.05$.^cSignificant difference between group A and group D, $P < 0.05$.^dSignificant difference between group D and groups A and B and between group C and group A.**Table 3.** Summary of Effectiveness: Degree of Relief

Baseline pain	Group A (25 μ g)	Group B (40 μ g)	Group C (55 μ g)	Group D (70 μ g)
VAS _{baseline}	4.7 \pm 2.0	2.9 \pm 1.0	4.0 \pm 1.7	5.0 \pm 2.4
MAXPID ^a	3.9 \pm 2.2	4.0 \pm 1.0	4.2 \pm 1.6	4.2 \pm 1.2
VAS _{min}	0.4 \pm 0.7	0.3 \pm 0.4	0.0 \pm 0.1	0.0 \pm 0.1
Patients achieving VAS < 1 cm (%)	80	100	100	100
VAS _{end}	4.0 \pm 7.3	4.9 \pm 2.0	4.5 \pm 1.4	5.1 \pm 2.0

All values except patients achieving VAS < 1 cm are mean \pm SD.^aMAXPID, maximum pain intensity difference (VAS) from baseline over the 8-h observation period (i.e., larger is better).

response with respect to duration of analgesia. Group D had a significantly longer duration than groups A and B ($P < 0.05$). Group C also had a longer duration of analgesia when compared with group A. There was no difference in duration of analgesia between groups C and D.

There were no intergroup differences in VAS pain scores at the time of request for additional analgesia (VAS_{end}). Twenty-four-hour parenteral narcotic requirements after request for additional analgesia were similar for all groups. Cumulative 24-h narcotic dosages were 38.8 \pm 20, 48.8 \pm 13, 46.5 \pm 23, and 46.0 \pm 18 mg for groups A, B, C, and D, respectively.

There were no significant differences between groups with regard to mean respiratory rate, which

averaged 16.8 \pm 4, 18.2 \pm 3, 16.5 \pm 3, and 17.4 \pm 3, respectively, for groups A, B, C, and D. Likewise, there were no significant group differences in sedation, with 47%, 48%, 39%, and 33% of patients in groups A, B, C, and D having a sedation score <1. As noted in Table 4, 20 of 41 patients (49%) experienced at least one side effect. The incidence per dose was as follows: group A, 36.4%; group B, 50%; group C, 50%; and group D, 60%. A single patient who received 70 μ g of sufentanil suffered profound respiratory depression which occurred within 5 min of the epidural injection. This patient required tracheal intubation and ventilatory support until the narcotic effect was sufficiently inhibited by intravenous naloxone. The epidural catheter was removed and closely inspected, revealing blood within the distal 2 cm of the catheter. This finding suggests a high probability of an intravascular injection. This patient was removed from the study, and another patient was randomized to take her place. Trends suggestive of increased nausea, vomiting, and pruritus with increasing sufentanil dose did not reach statistical significance (Table 4).

Discussion

Epidural sufentanil provides analgesia of rapid onset after lower abdominal surgery. The rapidity, reliability, and marked level of pain relief achieved were

Table 4. Adverse Experiences by Severity and Treatment Group

Adverse experience	Sufentanil (25 µg)				Sufentanil (40 µg)				Sufentanil (55 µg)				Sufentanil (70 µg)			
	Total incidence (%)		Severity ^a		Total incidence (%)		Severity ^a		Total incidence (%)		Severity ^a		Total incidence (%)		Severity ^a	
	Mild	Moderate	Severe		Mild	Moderate	Severe		Mild	Moderate	Severe		Mild	Moderate	Severe	
Total number of patients	11				10				10				10			
Number of patients with adverse experience																
Total	4 (36.4)				5 (50.0)				5 (50.0)				6 (60.0)			
Pruritus	2 (18.2)				1 (10.0)				3 (30.0)				3 (30.0)			
Vomiting	1 (9.1)				2 (20.0)				1 (10.0)				2 (20.0)			
Nausea	1 (9.1)				1 (10.0)				0				1 (10.0)			
Respiratory depression	0				0				2 (20.0)				3 (30.0)			
													0			

^aSeverity as judged by nurse observer.

particularly beneficial in the setting of this protocol where, at the time of administration, local anesthetic blockade had largely dissipated and VAS scores indicated moderate discomfort. Effective analgesia was achieved by all patients in the four treatment groups. The time to maximum pain relief was rapid, as evidenced by a decrease in the VAS scores to less than 1 cm within 20 min at the three highest dosages. Although duration of analgesia appeared to increase in response to increasing epidural doses, the use of doses larger than 40–55 µg does not seem to be warranted if other analgesic regimens are instituted within 3 h of sufentanil administration.

Our findings are in agreement with those of Donadoni et al. (1) in patients undergoing lower extremity orthopedic surgery. They found no improvement in the quality or duration of postoperative analgesia as the sufentanil dose was increased above 50 µg. Verbough et al. (10) achieved postoperative analgesia of approximately 4-h duration with sufentanil administered via thoracic or lumbar epidural catheters after upper or lower abdominal surgery but no increase in the duration of analgesia at dosages larger than 50 µg.

A number of alternative approaches have been proposed to extend safely the analgesia duration of sufentanil. The addition of epinephrine appears to decrease vascular absorption, resulting in prolonged epidural analgesia and reduced peak plasma concentration (5,8). Other studies (11–13) suggest the need to administer larger volumes of epidural injectate, as the rate of dural penetration and dermatomal spread of lipophilic opioids appear to be directly related to the surface area in contact with the drug. Continuous infusion techniques take advantage of sufentanil's rapid onset and short duration and may reduce respiratory risks associated with intermittent administration of large boluses. Cheng et al. (14) reported that continuous lumbar infusions of 0.3 µg·kg⁻¹·h⁻¹ provided rapid onset of sustained analgesia with minimal adverse effects in patients recovering from intraabdominal surgery. Another potential technique to extend the duration of effective analgesia is combining sufentanil with a reduced dose of a longer acting hydrophilic drug such as morphine.

Because potent lipophilic drugs such as sufentanil speed the time-course of clinically significant side effects, a conservative dosing regimen would seem warranted. In addition to the serious episode of respiratory depression that we observed with 70 µg, other reports of respiratory arrest have been observed after administration of large single boluses or repeat injections (7,8). As peak plasma levels of sufentanil are achieved within minutes of epidural administration (2), one must be alert for the "immediate onset" of respiratory depression. Given these concerns, we recommend the slow administration of sufentanil

(over a 3–5-min period) after careful aspiration. A clear occlusive dressing allows inspection of the epidural catheter as it exits the skin during aspiration. The rapid onset of sedation is an additional concern when higher doses of sufentanil are administered. Although marked sedation was not observed in any of the treatment groups, it is conceivable that the rapid increase in plasma levels and high potency of sufentanil might result in sedation of elderly or debilitated patients.

The incidence of nausea that we report is somewhat higher than that reported by previous investigators (1–3,14). This is partially explained by the extended observation period during which time the patients received parenteral opioids. Although high lipid solubility presumably confers some protection from centrally mediated side effects, rapid vascular absorption and cephalad migration within the cerebrospinal fluid may have contributed to the nausea and vomiting observed. Although we detected no significant differences in the overall incidence of side effects among the four treatment groups, the small number of patients within each group may have limited our ability to detect a dose-related increase in side effects.

We conclude that sufentanil in a dose range of 40–55 μ g provides rapid onset of epidural analgesia. This lasted for 2.5–3.5 h in the present population of healthy patients recovering from intraabdominal surgery and thereby provides an interval for initiation of longer term analgesic therapy. In light of sufentanil's high potency and rapid onset of action, this medication should be carefully administered under close observation.

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Low Concentrations of Isoflurane Abolish Motor Evoked Responses to Transcranial Electrical Stimulation During Nitrous Oxide/Opioid Anesthesia in Humans

Cor J. Kalkman, MD, John C. Drummond, MD, and Ariënné A. Ribberink, MD

Department of Anesthesiology, University of California at San Diego and VA Medical Center, San Diego, California;
Department of Anesthesiology, University of Amsterdam, The Netherlands

To study the feasibility of noninvasive monitoring of motor pathways in anesthetized patients, we evaluated the effect of isoflurane on motor evoked responses to constant-voltage transcranial electrical stimulation (tc^e-MERs). Reproducible tc^e-MERs were recordable from the tibialis anterior muscle during nitrous oxide/opioid anesthesia in 11 patients. Before the introduction of isoflurane, tc^e-MER onset latency was 30.8 ± 1.9 ms, and amplitude ranged from 19 μ V to 2.6 mV (median, 209 μ V). Operating conditions necessitated neuromuscular blockade in three patients before administration of isoflurane. In the

remaining eight patients, introduction of isoflurane in low concentrations resulted in an immediate increase in the latency and a decrease in the amplitude of tc^e-MERs. The tc^e-MERs were completely obliterated in all subjects at end-tidal isoflurane concentrations between 0.2% and 0.6% (median, 0.24%). After discontinuation of isoflurane, the tc^e-MER returned in all patients. The authors conclude that, during nitrous oxide/opioid anesthesia, with the stimulus and recording variables used, isoflurane even at very low concentrations precludes recording of tc^e-MERs.

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Because of concern regarding the possibility of "false-negative" somatosensory evoked responses (SSERs), techniques have been developed in an attempt to permit reliable monitoring of motor pathways in anesthetized patients. Both transcranial electric and transcranial magnetic stimuli have been used successfully to elicit motor evoked responses (MERs) during surgery (1,2). However, numerous anesthetics, including nitrous oxide (3), midazolam (4), fentanyl (5), thiamylal sodium (6), and volatile anesthetics (7) produce pronounced depression of MER amplitude. In particular, isoflurane is a potent depressant of motor evoked responses to transcranial electric stimulation (tc^e-MER) in rats (7). If this latter observation is applicable in humans, it may be particularly relevant because a nitrous oxide/opioid technique supplemented with low concentrations of isoflurane is commonly used for procedures in which SSERs are to be recorded. The same anes-

thetic might logically be considered if MERs were to be recorded in addition to SSERs. Accordingly, this study was undertaken to evaluate the effects of low concentrations of isoflurane on tc^e-MERs in humans anesthetized with a nitrous oxide/opioid combination.

Methods

The study was approved by the Human Subjects Committee of the University of California at San Diego. Written informed consent was obtained from 11 patients scheduled to undergo orthopedic surgical procedures. Exclusion criteria included a history of epilepsy, psychiatric disorder, or the use of any drugs known to lower seizure thresholds, e.g., tricyclic antidepressants and phenothiazines. All patients were ASA physical status I or II and were between 26 and 49 yr of age. Average height was 175 ± 9 cm and weight 84 ± 25 kg.

All patients received 2-4 mg of intravenous midazolam 10-15 min before entering the operating room. Anesthesia was induced with 5 mg/kg of sodium thiamylal ($n = 3$), 2 mg/kg of propofol ($n = 2$), or 0.3 mg/kg of etomidate ($n = 6$). Thirty seconds after loss of consciousness, tc^e-MERs were recorded in triplicate (tc^e-MERs were not recorded before induc-

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Address correspondence to Dr. Drummond, Neuroanesthesia Research, Mail Code 0629, University of California San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0629.

tion of anesthesia). Thereafter, 1–1.5 mg/kg of succinylcholine was administered to facilitate tracheal intubation. No other muscle relaxants were given during the surgical procedure unless the operating conditions necessitated neuromuscular blockade. In that event, the patient was excluded from the remainder of the study. An intravenous dose of 1 $\mu\text{g/kg}$ of sufentanil or 10 $\mu\text{g/kg}$ of fentanyl was administered before skin incision. Anesthesia was maintained with 66% nitrous oxide in oxygen and sufentanil ($n = 7$) or fentanyl ($n = 4$) by continuous infusion (sufentanil, 0.2–0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$; fentanyl, 2–3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$). All patients were mechanically ventilated using a semi-closed circle system and a fresh gas flow of 4 L/min. Ventilation was adjusted to maintain end-tidal CO_2 between 36 and 40 mm Hg. End-tidal isoflurane concentration was measured by mass spectrometry. At an interval of at least 30 min after induction of anesthesia, isoflurane was introduced at a dial setting of 0.5% with a fresh gas flow of 4 L/min. The inspired isoflurane concentration was adjusted such that the end-tidal concentration increased gradually (~ 10 min) toward a value of 0.3%. The tc^e -MERs were elicited in duplicate at intervals of 2 min during the washin. If a reproducible response was still recordable at an end-tidal isoflurane concentration of 0.3%, the inspired isoflurane concentration was adjusted upward to result in stepwise increments of end-tidal concentration of approximately 0.1% per 5 min. After at least 30 min of isoflurane administration, isoflurane was discontinued and the tc^e -MERs were recorded at 2-min intervals during isoflurane washout. When signs of light anesthesia occurred, a bolus dose of the original drug used for induction of anesthesia (50% of the induction dose) was given.

Transcranial electrical stimuli were delivered to the scalp via silver-silver chloride electroencephalographic disk electrodes with a diameter of 10 mm. The anode was placed at the vertex and the cathode was placed in the midline 7 cm anteriorly. Constant-voltage stimuli were delivered with a stimulator specifically designed for transcranial electrical stimulation (Digitimer D180A; Digitimer Ltd., Welwyn Garden City, U.K.). This stimulator delivers single stimuli of up to 1200 V with a user-selectable time constant of 50 or 100 μs . In the present investigation, the 100- μs time constant was used, and stimulus intensity was set at 50%–60% of maximum output (i.e., 600–750 V). Compound muscle action potentials to single stimuli were recorded from the left or right tibialis anterior muscle using Grass gold disk electrodes placed over the muscle in a belly/tendon fashion. The time base was 100 ms. Recordings were made with a Cadwell Quantum 84 evoked response analyzer (Cadwell Laboratories, Kennewick, Wash.). Amplifier gain was adjusted in accordance with the

amplitude of the compound muscle action potential signal to obtain maximum vertical resolution. The band pass filters (-3 -dB roll-off) were set at 10 and 3000 Hz. The waveforms were stored on magnetic disk. Latency and amplitude were measured using electronic cursors. The latency was defined as the time to the onset (initial deflection) of the response. Amplitude was defined as the maximum peak-to-peak deflection.

Latencies are presented as mean \pm SD. Compound muscle action potential amplitudes were not normally distributed and are therefore presented as medians and ranges. The following time points were compared: (A) 1 min after induction of anesthesia (but before administration of succinylcholine and opioid); (B) during maintenance of anesthesia with nitrous oxide/opioid at least 20 min after intubation; (C) immediately before administration of isoflurane; (D) 5 min after the end-tidal isoflurane concentration reached 0.3%; (E) when the end-tidal isoflurane concentration had been 0.0% for 1 min; and (F) when the end-tidal isoflurane concentration had been 0.0% for 15 min. In addition, the end-tidal isoflurane concentration at the time of the first unrecordable tc^e -MER was noted.

Amplitude differences between the various time-points were compared nonparametrically using Friedman's statistic. Latency data were compared using analysis of variance for repeated measures. A P -value less than 0.05 was considered significant.

Results

Reproducible tc^e -MERs were recordable immediately after induction of anesthesia in the six patients who received etomidate. The tc^e -MERs were not recordable immediately after induction of anesthesia in the two patients who received propofol and in one of the three patients who received thiamylal. However, in all patients, reproducible responses were subsequently recordable during nitrous oxide/opioid anesthesia (intervals B and C). In three patients a muscle relaxant was administered at the specific request of the surgeon because of difficulty in achieving access to the surgical field. Table 1 presents the individual mean tc^e -MER amplitudes at the various intervals. At interval C, during maintenance of anesthesia with nitrous oxide/opioid before administration of isoflurane, the average latency of the first deflection of the tc^e -MER was 30.8 ± 1.9 ms and the median amplitude was 209 μV (range 19–2682 μV). There was considerable variability in amplitude between subjects. For instance, during maintenance of anesthesia with nitrous oxide/opioid (interval B), amplitude ranged from 46 to 2383 μV . Amplitudes were also extremely variable within some patients. In three of the eight

Table 1. Amplitudes in Microvolts of Intraoperative Motor Evoked Responses to Transcranial Electrical Stimulation During Nitrous Oxide/Opioid Anesthesia, Before, During, and After Administration of Isoflurane

Patient No.	Induction agent	Opioid	Intervals ^a						No response ET-isoflurane ^b (%)
			A Postinduction	B N ₂ O/opioid	C N ₂ O/opioid	D 0.3% isoflurane	E 0.0% isoflurane (1 min)	F 0.0% isoflurane (15 min)	
1	P	F	0	46	32	R	R	R	R
2	T	S	0	147	R	R	R	R	R
3	E	S	178	293	291	0	0	221	0.20
4	E	S	2500	2383	2682	0	1765	1546	0.27
5	T	S	234	52	80	0	9	R	0.20
6	E	S	278	185	413	0	45	27	0.21
7	T	S	343	53	19	0	0	11	0.30
8	E	F	362	83	64	R	R	R	R
9	E	F	1400	109	127	0	0	84	0.20
10	P	S	0	340	360	250	422	684	0.60
11	E	F	285	291	387	0	ND	ND	0.30
Median			278	147	209	0	0	127	0.24

P, propofol; T, thiamylal sodium; E, etomidate; F, fentanyl; S, sufentanil; R, muscle relaxant given; ND, no data.

^aIntraoperative intervals: A, immediately after induction agent; B, during nitrous oxide/opioid infusion; C, during nitrous oxide/opioid infusion immediately before isoflurane administration; D, 5 min after end-tidal concentration reached 0.3%; E, 1 min after end-tidal isoflurane concentration reached 0.0%; F, 15 min after end-tidal isoflurane concentration reached 0.0%.

^bEnd-tidal isoflurane concentration at which no motor evoked response could be recorded.

patients, amplitude variability (expressed as the coefficient of variation calculated over eight successive tc^e-MER waveforms recorded at 2-min intervals) was greater than 50% before introduction of isoflurane. There were no significant differences in amplitude or onset latency between the postinduction values (interval A) and those recorded either during maintenance of anesthesia with nitrous oxide/opioid (interval B) or before administration of isoflurane (interval C). Isoflurane was introduced before skin incision in two patients and after skin incision in the remaining six. Surgical stimulation was ongoing in all patients at the time the tc^e-MER was lost.

Introduction of isoflurane resulted in an immediate decrease in tc^e-MER amplitude in all patients. The tc^e-MER was abolished at a median end-tidal isoflurane concentration of 0.24% (range 0.20%–0.60%). The amplitude of the tc^e-MER before isoflurane administration bore no apparent relationship to the concentration at which the response was abolished. For instance, in the patient with the largest preisoflurane tc^e-MER amplitude (patient 4), the tc^e-MER was unrecordable at an end-tidal isoflurane concentration of 0.27%. Latencies were increased by 1–3 ms ($P < 0.05$) before the response was lost. After discontinuation of isoflurane, the tc^e-MER returned in all patients. There are no tc^e-MER data during isoflurane washout in patient 11 because discontinuation of isoflurane was not feasible. Figure 1 shows tc^e-MER waveforms before, during, and after administration of isoflurane in patient 4, who had the largest amplitudes during maintenance of anesthesia with nitrous

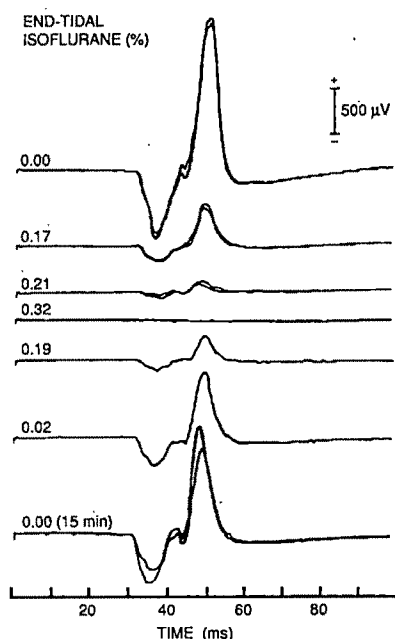


Figure 1. Motor evoked responses to transcranial electrical stimulation in patient 4 during nitrous oxide/sufentanil anesthesia before, during, and after administration of isoflurane (0.3% end-tidal). Duplicate waveforms are superimposed to show reproducibility, except during recovery (isoflurane concentrations 0.19% and 0.02%) when only one waveform was recorded.

oxide/sufentanil. Figure 2 shows the time-course of the end-tidal isoflurane concentration and tc^e-MER amplitude changes in the same patient. In some patients there was apparent hysteresis in that the

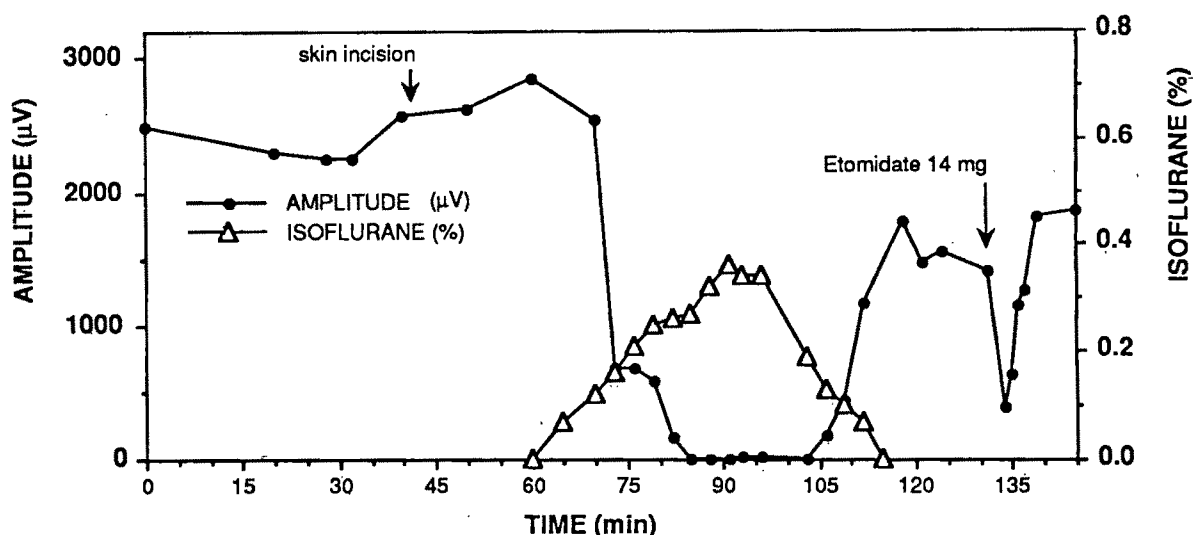


Figure 2. Amplitude (μV) of motor evoked responses to transcranial electrical stimulation and end-tidal isoflurane concentration versus time in patient 4 during nitrous oxide/sufentanil anesthesia.

tc^e-MERs were of lower amplitude at a given end-tidal isoflurane concentration during washout than during washin, and the responses continued to recover even after the end-tidal concentration was zero.

In patients 5 and 6, clinical signs of light anesthesia after discontinuation of isoflurane were preceded by "giant" motor responses (a sudden threefold to fivefold amplitude increase as compared with the immediately preceding response). The effect of the supplementary bolus doses of the original induction agent was in general a small increase in tc^e-MER latency and a substantial decrease in amplitude. For instance, in patient 4, a 0.2-mg/kg bolus dose of etomidate decreased amplitude from 1546 to 390 μV (Figure 2). In patient 7, a bolus dose of 200 mg of thiamylal abolished the tc^e-MER for 6 min.

Discussion

The results of the present investigation indicate that isoflurane is an extremely potent depressant of tc^e-MER amplitude when superimposed on a background anesthetic of nitrous oxide combined with fentanyl or sufentanil. In four patients, the tc^e-MER waveform was abolished at end-tidal isoflurane concentrations of 0.2% or less. Haghighi et al. (7) studied the effects of increasing concentrations of isoflurane, enflurane, or halothane from 0.5% to 1.5% on the forelimb compound muscle action potential in response to direct electrical stimulation of the exposed motor cortex in rats anesthetized with fentanyl and droperidol. All volatile agents caused a progressive increase in onset latency and a decrease in peak-to-peak amplitude to less than 10% of baseline. Most of

the amplitude depression occurred between 0% and 0.5%. However, the response was recordable (23–103 μV) at 1.5% of either agent. The apparently greater sensitivity to the suppressant effects of isoflurane in our human subjects may be the result of additive effects of isoflurane and nitrous oxide, or may be due to differences in locus and intensity of stimulus.

Neither the site nor the precise mechanisms of the effects of isoflurane on tc^e-MERs is known. There are several possibilities. Isoflurane may alter stimulus thresholds of the pyramidal cells in the motor cortex, influence axonal conduction along the corticospinal tract, reduce the responsivity of α -motor neurons in the anterior horn of the spinal cord, and/or decrease transmission along the peripheral nerve and through the myoneural junction. While the peripheral mechanisms probably make at most minor contributions at low concentrations of isoflurane, the relevant central mechanisms have not been defined.

There was probably already some degree of tc^e-MER depression before the introduction of isoflurane. The patients in the present study had received midazolam, thiamylal, propofol, or etomidate and nitrous oxide with fentanyl or sufentanil before the tc^e-MER recordings that preceded administration of isoflurane. In volunteers, a continuous infusion of midazolam, 0.3 mg·kg⁻¹·h⁻¹ for up to 30 min, caused a progressive decrease of the amplitude and duration of MER to transcranial magnetic stimulation (4). Nitrous oxide depresses tc^e-MER amplitude. Zentner et al. observed tc^e-MER (hand area) amplitude reductions to 9% of baseline values in healthy volunteers breathing 66% nitrous oxide (3). In the same study, the authors reported that during maintenance of

anesthesia with nitrous oxide and fentanyl, amplitudes of tc^e-MER from the anterior tibial muscles were reduced to an average of 7% of the awake baseline values, which ranged from 600 μ V to 3.6 mV. The foregoing information, though incomplete, indicates that anesthetics have varied and substantial influences on tc-MERs. Accordingly, tc^e-MERs might have been recordable at greater end-tidal concentrations of isoflurane if the background anesthesia had been accomplished with other anesthetics.

Our findings may have considerable clinical significance. Isoflurane, in concentrations up to 0.5%, is commonly used to supplement an opioid/nitrous oxide-based anesthetic technique in order to reduce opioid requirements and to prevent intraoperative awareness. This regimen, with minor variations, is among the most commonly used anesthetic techniques in the United States today and is widely employed when SSER recording is performed. However, the present data suggest that the suppressive effect of isoflurane on MERs is probably much greater than its effect on SSERs. It has been demonstrated that in neurologically intact patients, end-tidal concentrations of 0.5 MAC halothane, enflurane, or isoflurane (each in 60% nitrous oxide) are compatible with effective SSER monitoring (8,9). Although reliable SSER monitoring is possible when isoflurane is used in these concentrations, our results suggest that intraoperative tc^e-MER monitoring will be impossible when even low concentrations of isoflurane are used to supplement opioid/nitrous oxide anesthesia.

As transcranial electrical stimulation is uncomfortable, we did not attempt to record awake baseline tc^e-MERs. Therefore no conclusions with respect to the effects of the drugs used for induction of anesthesia can be drawn from the immediate postinduction values. However, our very limited experience with responses to intravenous bolus administration of thiamylal, propofol, and etomidate suggests that intraoperative tc^e-MER amplitude may be better preserved after etomidate than after propofol or thiamylal. There have been no other comparisons of the effects of these agents on tc^e-MERs. However, repeated doses of etomidate produced only mild reduction of amplitude (up to 50%) of tc-MERs to magnetic transcranial stimulation (tc^{mag}-MERs) in monkeys (10), whereas thiamylal produced severe depression (6). Etomidate is unique among anesthetics in that its administration is associated with an *increase* in the amplitude of cortical SSERs (11). Given the inevitable differences in the neural pathways involved in SSERs and MERs, it should not be assumed that etomidate will also be more suitable for use when MER recording is performed. However, our nonsystematic experience with etomidate in the present investigation

suggests that this possibility is worthy of more detailed evaluation.

Several factors influence the amplitudes of tc-MERs in awake subjects and may have contributed to the substantial amplitude variability that was observed. Voluntary contraction of the muscle studied may dramatically "facilitate" (i.e., increase the amplitude of) both tc^e- and tc^{mag}-MERs (12,13). Facilitation of tc-MERs has even been observed in muscles in the period immediately preceding the onset of voluntary contraction (14) and after prior somatosensory (15) or mechanical stimuli (16). The large variability between successive responses observed in some of our patients is unlike the relative constancy of SSERs during steady-state anesthesia and may make interpretation of MERs somewhat more difficult. In particular, our observation that a sudden threefold to fivefold increase of tc^e-MER amplitude may occur as a result of light anesthesia suggests that facilitation of tc^e-MER may also occur in "anesthetized" patients and may complicate interpretation of amplitude changes. The practical consequence of this inherent tc^e-MER amplitude variability is that the generally accepted criteria for critical alteration during SSER monitoring, e.g., a 50% decrease in amplitude, will not be applied to tc^e-MERs unless intraoperative variability can be reduced.

In the present investigation, tc^e-MER to *single* stimuli were recorded. Zentner et al. (3), who observed considerable depression of tc^e-MER during anesthesia with nitrous oxide and fentanyl, suggested that averaging 5–15 responses might improve intraoperative recordability. In our patients, during maintenance of anesthesia with nitrous oxide/opioid, tc^e-MER amplitudes ranged from 19 μ V to more than 2.5 mV. As a result, the signal-to-noise ratio was such that, before the introduction of isoflurane, signal averaging was unnecessary. Averaging several tc^e-MER to single stimuli might have resulted in the ability to identify responses at isoflurane concentrations at which they were undetectable after single stimuli. However, the apparent dose-response relationship between isoflurane concentration and amplitude was sufficiently "steep" that it seems unlikely that detectable responses could have been present at concentrations appreciably higher than the limits we observed. There is an additional consideration. The single stimulus technique serves to minimize the total number of stimuli delivered to the patient intraoperatively. Although no adverse effects of repeated electrical or magnetic transcranial stimulation have been reported to date (17–20), the total number of stimuli delivered intraoperatively should be limited pending a more long-term experience.

We conclude that tc^e-MERs can be recorded readily during anesthesia with nitrous oxide and either

fentanyl or sufentanil. However, the addition of isoflurane in expired concentrations of 0.2%–0.3% is sufficient to completely abolish tc^e-MER waveforms in the majority of patients. The results indicate that isoflurane supplementation of nitrous oxide/opioid anesthesia is incompatible with the intraoperative monitoring of tc^e-MERs with the techniques used in the present study.

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A Comparison of Cerebral Blood Flow Reactivity to CO₂ During Halothane Versus Isoflurane Anesthesia for Carotid Endarterectomy

William L. Young, MD, Isak Prohovnik, PhD, James W. Correll, MD,
Noeleen Ostapovich, REEGT, Eugene Ornstein, PhD, MD, and Donald O. Quest, MD

Departments of Anesthesiology, Psychiatry, Neurology, Radiology, and Neurological Surgery, Columbia University College of Physicians and Surgeons, New York, New York

The effects of isoflurane or halothane on cerebral blood flow (CBF) reactivity to changes in arterial carbon dioxide tension (Paco₂) during carotid endarterectomy were compared using the intravenous method of ¹³³Xe-CBF determination. Patients, aged 65 ± 3 yr (mean ± SE), received O₂ and N₂O (1:1) and either 0.75% isoflurane (*n* = 7) or 0.5% halothane (*n* = 7). Patient demographic and clinical data were similar for both groups and followed the expected strata of patients with ischemic cerebrovascular disease. Measurements were made during the period of temporary bypass shunting. In the isoflurane group, increasing Paco₂ from 33.3 ± 1.4 to 43.4 ± 1.3 mm Hg resulted in a significant (*P* < 0.05) increase in CBF

from 21 ± 1 to 35 ± 4 mL·100 g⁻¹·min⁻¹. In the halothane group, increasing Paco₂ from 31.1 ± 1 to 39.4 ± 1.6 mm Hg resulted in a significant increase in CBF from 26 ± 3 to 37 ± 3 mL·100 g⁻¹·min⁻¹. Mean CBF reactivity to changes in Paco₂ (mL·100 g⁻¹·min⁻¹·mm Hg⁻¹) was 1.74 ± 0.39 for isoflurane and 1.78 ± 0.4 for halothane (not significant), corresponding to a relative change of 4.8% ± 0.8% and 5.2% ± 1.3% per mm Hg, respectively. There is no significant difference between halothane and isoflurane in their effects on CO₂ reactivity in the mildly hypocapnic to normocapnic range.

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The effect of anesthetic agents on the response of the cerebral circulation to changes in arterial carbon dioxide tension (Paco₂) may have implications for the acute intraoperative management of cerebral ischemia (1). There may be some benefit in the application of hypocarbia in the setting of focal cerebral ischemia, presumably on the basis of an "inverse steal" phenomenon, but the issue is controversial (1). Based on animal studies (2,3), isoflurane and halothane may have different effects on cerebrovascular reactivity to CO₂. If isoflurane results in a greater degree of CO₂ reactivity than halothane does, this could be a theoretical consideration favoring its use in the setting of focal cerebral ischemia. It would be useful to know if this difference is apparent in the usual range of anesthetic concentrations and Paco₂

levels used in patients undergoing carotid endarterectomy, an operation that entails an appreciable risk of cerebral ischemic complications. This study was undertaken to compare cerebral blood flow (CBF) reactivity to changes in Paco₂ during halothane or isoflurane anesthesia in the presence of N₂O and O₂.

Methods

After institutional approval, informed consent was obtained from patients scheduled to undergo elective carotid endarterectomy. All patients received a standard premedication of atropine (0.4 mg) and diazepam (10 mg). Anesthesia was induced with midazolam (0.04 mg/kg) and thiopental (4 mg/kg), with tracheal intubation facilitated by vecuronium (0.1-0.2 mg/kg). Patients were randomly assigned on an alternating basis to receive either 0.75% isoflurane (inspired concentration) in 1:1 N₂O/O₂ (*n* = 7) or halothane, 0.5% in 1:1 N₂O/O₂ (*n* = 7). Monitoring included the use of a radial artery catheter for arterial blood pressure measurement and blood gas analysis, a temperature probe, a capnograph, and a pulse oximeter. After arteriotomy, all patients had a temporary indwelling carotid shunt

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Address correspondence to Dr. Young, Department of Anesthesiology AP 901, 161 Fort Washington Avenue, New York, NY 10032.

Table 1. Study Population Characteristics

	Isoflurane (n = 7)	Halothane (n = 7)
Age (yr)	65 ± 5	68 ± 3
Sex (female/male)	4/3	5/2
Site (left/right)	2/5	4/3
Risk group (high/low)	5/2	4/3
Hypertension	7/7	5/7
Diabetes mellitus	2/7	2/7
Coronary artery disease	2/7	2/7
Prior cerebrovascular accident	3/7	3/7

All differences are not significant. Age expressed as mean ± SE. Risk groups refer to the system described by Sundt et al. (9). High-risk patients were in the Sundt et al. groups 3 and 4 and low-risk patients were in Sundt et al. groups 1 and 2.

inserted. Approximately 10 min after reestablishment of carotid blood flow following shunt insertion, a baseline CBF measurement was obtained (Cerebrograph 10a, Novo Diagnostic Systems, Bagsvaerd, Denmark) as previously described (4-6). Briefly, 10-20 mCi of ¹³³Xe in sterile saline solution was injected intravenously. A small plastic catheter was present in the endotracheal tube for sampling of end-tidal gas to determine tracer activity, and the resultant air activity curve was used to deconvolute the head curves and to correct for recirculation of tracer. Clearance was recorded for 11 min. The end-tidal CO₂ tension (P_{ET}CO₂) was then increased 10 mm Hg by addition of CO₂ to the inspired gas mixture. After 10 min at a stable P_{ET}CO₂ level (during which time residual remaining ¹³³Xe activity was registered from the head detectors), CBF was again measured. The P_{ET}CO₂ levels were verified by arterial blood gas determination for PaCO₂. The two measurements at different levels of PaCO₂ were used to calculate CBF reactivity. The CBF data are expressed as the Initial Slope Index in mL·100 g⁻¹·min⁻¹ assuming a xenon blood-brain partition coefficient of unity for the perfused tissue (7,8). The mean of the 10 CBF detectors covering both middle cerebral artery supply territories was taken as an index of global CBF. The global CBF reactivity to CO₂ was calculated as both the absolute increases in CBF in per millimeter of mercury-change in PaCO₂ (mL·100 g⁻¹·min⁻¹·mm Hg⁻¹) and the percentage increase in CBF per millimeter of mercury increase in PaCO₂.

Using the grading system described by Sundt et al. (9), patients were categorized into four preoperative risk groups based on angiographic findings, neurologic status, and general health: groups 1 and 2 were considered low risk, and groups 3 and 4 were considered high risk (Table 1).

Data were compared using two-way repeated measures analysis of variance (ANOVA) with anesthetic agent as the between-group factor and with CBF before and after CO₂ challenge as the repeated with-

in-group measure. If there were significant differences, post hoc testing was done using the Fisher protected least significant differences test. Nonparametric data were compared using contingency χ^2 analysis. The threshold for significance was taken as $P < 0.05$. All results are expressed as mean ± SE.

Results

The anesthetic groups appeared to be equivalent with respect to preexisting medical and neurologic condition. Demographic data are presented in Table 1; by χ^2 analysis there was no difference between anesthetic groups. One patient in the isoflurane group emerged from the anesthetized state with mild aphasia and hemiparesis that resolved by the next day. Global CBF and other physiologic results are summarized in Table 2. There were no differences between physiologic variables between anesthetic groups at either baseline or CO₂ challenge except for hemoglobin concentration, which was significantly lower for the halothane group. Between baseline and CO₂ challenge conditions, there were no differences in variables except for PaCO₂, P_{ET}CO₂, and CBF, which were significantly higher during addition of CO₂ to the inspired gas mixture. Although baseline CBF tended to be higher for halothane, it did not achieve statistical significance. Mean CBF reactivity to changes in PaCO₂ (mL·100 g⁻¹·min⁻¹·mm Hg⁻¹) was 1.74 ± 0.39 for isoflurane and 1.78 ± 0.40 for halothane. These values correspond to a relative change of 4.8 ± 0.8 and 5.2 ± 1.3 % change/mm Hg, respectively. There was a trend for CBF and cerebrovascular reactivity to CO₂ to be greater in the low-risk versus high-risk groups, but this did not reach significance (6.1 ± 1.7 versus 4.0 ± 0.8 % change/mm Hg).

Discussion

In this study we have shown that, within the range of PaCO₂ commonly used during anesthetic management of carotid endarterectomy, there is little difference between isoflurane and halothane in global CBF reactivity to changes in CO₂ tension. Given the small sample size in each group ($n = 7$), consideration of the power of our negative findings is relevant. Even the small differences in CO₂ reactivity that we observed between isoflurane and halothane may achieve statistical significance with sufficiently large sample sizes. If means and variances remain largely unchanged, CO₂ reactivity during isoflurane anesthesia would be significantly lower in absolute terms if both samples had about 550 patients, whereas relative reactivity would achieve significance at a sample size of about 40. However, it was our aim to investigate clinically meaningful differences, and the small

Table 2. Physiologic Variables for Isoflurane and Halothane During Baseline and After CO₂ Challenge

	Baseline		CO ₂ challenge	
	Isoflurane (n = 7)	Halothane (n = 7)	Isoflurane (n = 7)	Halothane (n = 7)
CBF (mL·100 g ⁻¹ ·min ⁻¹)	21 ± 1	26 ± 3	35 ± 4 ^a	37 ± 3 ^a
Mean arterial pressure (mm Hg)	105 ± 7	102 ± 4	94 ± 5	97 ± 5
pH	7.45 ± 0.02	7.48 ± 0.01	7.39 ± 0.02 ^a	7.40 ± 0.02 ^a
Paco ₂ (mm Hg)	33.3 ± 1.4	31.1 ± 1	43.4 ± 1.3 ^a	39.4 ± 1.6 ^a
PETCO ₂ (mm Hg)	25 ± 1	25 ± 1	34 ± 1 ^a	34 ± 2 ^a
Pao ₂ (mm Hg)	196 ± 20	216 ± 13	194 ± 11	202 ± 20
Hemoglobin (mg/dL)	14.0 ± 0.8	11.4 ± 0.8 ^b	13.9 ± 0.8	11.5 ± 0.7 ^b
Temperature (°C)	35.5 ± 0.2	35.7 ± 0.2	35.7 ± 0.1	35.8 ± 0.1
Slope of CBF response (mL·100 g ⁻¹ ·min ⁻¹ ·mm Hg ⁻¹)			1.74 ± 0.39	1.78 ± 0.40
% Change in CBF (%/mm Hg)			4.8 ± 0.8	5.2 ± 1.3

CBF, cerebral blood flow; Paco₂, arterial CO₂ tension; PETCO₂, end-tidal CO₂ tension; Pao₂, arterial O₂ tension.^aSignificantly different from baseline.^bSignificantly different from isoflurane.

effects observed here should not affect practical management of Paco₂ regardless of statistical significance.

Using intraarterial ¹³³Xe washout in the cat (2) and using hydrogen clearance in the rabbit (3), isoflurane enhanced CO₂ responsiveness compared with halothane. However, in a canine venous outflow preparation using 1 MAC (1.4%) isoflurane, the CBF response slope of between 30 and 40 mm Hg was approximately 2 mL·100 g⁻¹·min⁻¹·mm Hg⁻¹ and there appeared to be no quantitative difference between this slope and previous studies of halothane by the same group (10). McPherson et al. (11) demonstrated a similar slope in the dog using the microsphere method for CBF determination under identical anesthetic conditions.

There have been no previous comparisons between isoflurane and halothane CBF reactivity to CO₂ in humans, but our values compare favorably with other separate reports in humans receiving one agent or the other. These data have been compared in Table 3 and Figure 1, which illustrate that several different studies of either isoflurane or halothane, using different methodologies, yield quantitatively similar slopes of the CO₂ response line.

The choice of anesthetic agent for use during an operation that entails risk of cerebral ischemia remains a debated topic. In animal investigations, no difference exists between isoflurane and halothane with regard to cerebral protection using neurologic outcome as an endpoint after middle cerebral artery occlusion (12) or after unilateral carotid occlusion and hypotension (13). However, in retrospective clinical studies that examine the incidence of cerebral ischemia during carotid occlusion, the use of isoflurane has been associated with fewer ischemic electroencephalographic changes than halothane (14,15).

These studies suggest that the blood flow threshold, below which cerebral ischemia develops, is lower for isoflurane than for halothane. Although halothane is a vasodilator relative to isoflurane in humans undergoing carotid endarterectomy in the presence of N₂O (4,14), there is no significant difference in its effect on cerebral metabolic rate for oxygen (4). Therefore, one could speculate that the mechanism of the observed electrophysiologic differences between the two agents resulting in different frequencies of cerebral ischemia may be related primarily to cerebrovascular effects, i.e., halothane may induce a greater degree of "cerebral steal."

Differences in CBF reactivity to CO₂ may have importance concerning the relative ability of different anesthetic regimens to influence the outcome from cerebral ischemia by hemodynamic mechanisms, i.e., inverse or "Robin Hood" steal, as recently reviewed by Artru and Merriman (1). The animal studies are few and contradictory (16-18). In humans undergoing endarterectomy, hypocapnia is capable of producing an increase in carotid back-pressure compared with normocapnia (19,20). Although not achieving statistical significance, hypocapnia has been associated with a trend for improved outcome at little additional risk to the patient during carotid endarterectomy (19,21) and to patients suffering thromboembolic stroke (22). Most important, it appears that the acute institution of hypocapnia in the setting of new cerebral ischemia during carotid endarterectomy may be associated with electroencephalographic signs of improved cerebral perfusion (1).

Although the absolute measured values for CBF in the halothane group tended to be higher than in the isoflurane group, this did not achieve statistical significance. That halothane did not result in higher CBF

Table 3. Summary of Studies Examining CO₂ Reactivity in Humans During General Anesthesia

Study	Population	n	CBF method	Anesthesia	Notes
Wollman et al. (28)	Normal	13	Kety-Schmidt	1.2% halothane in O ₂	See Figure 1
McHenry et al. (29)	Normal	8	Kety-Schmidt	1.0% halothane in 1:1 N ₂ O/O ₂	CO ₂ response slope of 1.84 (mL·100 g ⁻¹ ·min ⁻¹ ·mm Hg ⁻¹) (not shown in Figure 1)
Waltz et al. (30)	Carotid endarterectomy	5	Intracarotid ¹³³ Xe	Halothane in N ₂ O/O ₂	See Figure 1 One patient had recent onset of severe neurologic deficit with a decrease in CBF during CO ₂ challenge and data not included in Figure 1
Madsen et al. (31)	Craniotomy for tumor	7	Kety-Schmidt/ Δ AVDO ₂ ^a	0.75% isoflurane in 3:2 N ₂ O/O ₂	See Figure 1 Relative CO ₂ reactivity of 4.4 \pm 1.0% change/mm Hg and hypocapnic values in Figure 1 are extrapolated
Madsen et al. (32)	Craniotomy for tumor	7	Kety-Schmidt/ Δ AVDO ₂ ^a	0.45% halothane in 3:2 N ₂ O/O ₂	Relative CO ₂ reactivity of 5.1%, but did not report the actual range of CO ₂ tested (not shown in Figure 1)
Young et al. (6)	Carotid endarterectomy	7	IV ¹³³ Xe	0.75% isoflurane in 1:1 N ₂ O/O ₂	See Figure 1
Young et al. (33)	Normal	7	IV ¹³³ Xe	0.75% isoflurane in 3:2 N ₂ O/O ₂	See Figure 1
Young et al. (33)	Craniotomy for arteriovenous malformation resection	26	IV ¹³³ Xe	0.75% isoflurane in 3:2 N ₂ O/O ₂	See Figure 1

CBF, cerebral blood flow; IV, intravenous.

^aChange in arteriovenous difference in oxygen content.

values in the present study, in contradistinction to previous studies in humans (4,14,23), may be due to insufficient statistical power in the small sample size in this study and to a slightly different range of PaCO₂ tested for each agent. There was also an unexpected significant difference between hemoglobin concentrations of the two groups, with the concentration of the halothane group being significantly lower than that of the isoflurane group. However, this would have the effect of overestimating the real difference in CBF between anesthetic groups.

Hansen et al. (24) have recently suggested that the differing effects of halothane and isoflurane on CBF previously reported are in part due to the method of measurement. They proposed that methods that measure only cortical flow will show a marked difference in CBF between the two agents, whereas whole-brain-weighted measures will not. This may be due to the preferential vasodilation in cortical versus subcortical regions found with halothane, at least in the rat. In a further study, Hansen et al. (25) attributed this difference to a selective effect of isoflurane

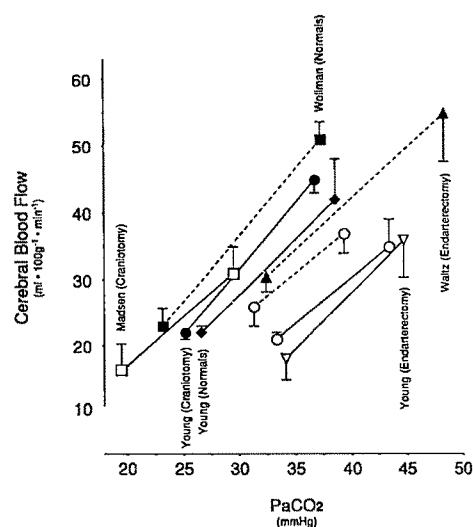


Figure 1. Comparison of cerebrovascular reactivity to CO₂ in selected human studies (see Table 3). The solid lines represent isoflurane and the dashed lines represent halothane. The results of the present study are indicated by the unlabeled open circles. Error bars represent SE. See Table 3 for further explanation.

to depress cortical metabolism. Although the intravenous method of ¹³³Xe-CBF determination preferentially looks at cortical blood flow, the use of the Initial Slope Index during lower flow states (such as during general anesthesia) does include washout from deeper, lower flow structures (5,8). The site and method of measurement will also influence the reported CO₂ reactivity (26). In the rat, however, halothane increases cortical flow relative to isoflurane, but cortical CO₂ reactivity is the same for both agents (27).

We conclude that in elderly patients undergoing carotid endarterectomy there is no significant difference in the effects of relatively low concentrations of halothane or isoflurane in NO₂ on CO₂ reactivity in the range studied. Therefore, we cannot recommend the preferential use of halothane or isoflurane for anesthetic management during carotid endarterectomy on this basis. With the exception of halothane in N₂O resulting in higher baseline CBF values (4), it appears that the cerebral metabolic rate of oxygen and cerebrovascular reactivity are similar for isoflurane, halothane, and narcotic anesthetic regimens that include N₂O (4,6). In the absence of any clear-cut neuroprotective effects for any particular anesthetic technique, it seems reasonable to not avoid use of any one of them if there is some concern about systemic cardiovascular effects, e.g., tachycardia in a patient with symptomatic angina pectoris given isoflurane anesthesia. This is especially pertinent to the patient undergoing carotid endarterectomy because of the high incidence of concomitant coronary arteriosclerotic disease.

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Respiratory Function and Ribcage Contribution to Ventilation in Body Positions Commonly Used During Anesthesia

Andrew B. Lumb, MB, BS, FCAnaes, and John F. Nunn, MD, PhD, FFARCS

Division of Anaesthesia, Clinical Research Centre, Middlesex, England

Lung function tests are normally performed in the upright position, whereas anesthesia is usually administered with the patient in the supine position, and occasionally in other postures. We therefore compared forced vital capacity (FVC), forced expiratory volume in 1 s (FEV₁), functional residual capacity (FRC), and ribcage contribution to ventilation by respiratory inductive plethysmography in 13 conscious healthy male volunteers, sitting and in four horizontal positions used during anesthesia. Forced vital capacity and FEV₁ were similar in all positions, except for a significant mean increase in FVC of 300 mL (sd 213) when sitting compared with when supine ($P < 0.001$). The mean decrease in FRC was 806 mL (sd 293) between the sitting and supine positions ($P < 0.001$). A significant increase in FRC occurred (252 mL, sd 329, $P < 0.01$) when supine

subjects raised their arms above their heads as required for computed tomography. Functional residual capacity in the prone and lateral positions was significantly larger than in the supine position (mean change 350 mL, $P < 0.001$), but was still some 450 mL less than in the sitting position. Mean ribcage contribution was similar in all horizontal positions (32%–36%), whereas supine values were significantly different from those of the sitting position (mean 70%, sd 11, $P < 0.001$). In conclusion, the various horizontal postures studied have no effect on FVC, FEV₁, or ribcage contribution to ventilation. However, FRC in the prone, lateral, and arms-up positions is on average 250 mL larger than in the supine position, an observation that may affect gas exchange during anesthesia in these positions.

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Whereas preoperative lung function tests are usually performed in the upright position, most anesthesia is administered to supine patients, and to a lesser extent to patients in the prone and lateral positions. For example, in thoracic anesthesia the lateral position is very common and the lung function of the patients is often poor. Also of interest is the supine position with the arms raised above the head. We do not know of this position being used in routine anesthesia, but it is essential in studies of anesthesia on the respiratory system that include computed tomography (CT) scanning of the chest (1).

The average contribution of the ribcage (RC) to total ventilation decreases from 60% to 35% on lying down (2), probably due to increased fiber length of the diaphragm which results in a stronger contraction. Assessment of RC contribution by measurement

of cross-sectional areas of the chest and abdomen has not previously been performed in positions such as the prone and lateral ones. This may provide more accurate results than measuring anteroposterior or lateral diameters because of the body cavity distortion that may occur in these positions.

Functional residual capacity (FRC) has been studied in many positions, including the prone position (3), but not in the lateral and arms-up positions. Similarly, though vital capacity has been studied in postures such as sitting, supine, and prone (3), there is a paucity of information on the effect of posture on "bedside" lung function tests such as forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV₁). We therefore studied respiratory function including FRC and the RC contribution to ventilation in these different positions using awake volunteers.

Methods

Thirteen healthy male subjects were studied with their informed consent after approval had been ob-

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Address correspondence to Dr. Lumb, Division of Anaesthesia, Clinical Research Centre, Watford Road, Harrow, Middlesex, HA1 3UJ, England.

Table 1. Subject Data

Subject	Age (yr)	Height (cm)	Weight (kg)	Sitting			
				FVC (L _{BTPS})	FEV ₁ (L _{BTPS})	FRC (L _{BTPS})	%RC
1	64	170	68	3.85	2.31	2.56	88
2	27	178	72	5.77	4.64	4.16	67
3	27	188	67	6.08	4.48	3.92	66
4	51	169	64	4.86	4.10	2.55	74
5	34	183	72	4.91	4.46	2.20	87
6	28	185	70	4.15	3.73	3.11	66
7	27	192	86	5.94	2.98	3.96	57
8	24	180	67	4.90	4.25	2.30	59
9	27	169	68	3.96	3.32	1.72	66
10	28	174	67	3.97	3.91	1.56	77
11	35	185	67	6.09	2.77	3.21	58
12	28	183	94	6.08	4.66	2.40	81
13	44	182	76	4.56	3.62	4.17	61
Mean	34.1	179.8	72.1	5.01	3.79	2.91	69.7
SD	11.8	7.1	8.3	0.89	0.76	0.92	10.6

BTPS, converted to body temperature and pressure saturated; FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; %RC, percentage contribution of ribcage to ventilation.

tained from the local ethical committee. The subjects had no history of respiratory disease and were not obese (obesity defined as a body mass index of >29). All were staff members of the hospital or research departments of anesthesia and so were familiar with breathing through a mouthpiece, but only three were familiar with the aims of the study. Their physical characteristics are shown in Table 1.

Each subject was studied in the morning at least 2 h after consuming a light breakfast without beverages containing stimulants. Throughout the study the subjects were distracted by headphones playing music of their choice.

All ventilatory measurements were made with a valveless closed circle system (Figure 1) incorporating a circulating fan (35 L/min) and an 8-L wet spirometer. The subject could be connected to the circuit with the tap open either to room air or the spirometer. Gas was continuously sampled at 500 mL/min from the inspiratory limb and returned to the circuit via a katharometer to measure the helium concentration and a paramagnetic oxygen analyzer. The katharometer displayed the helium concentration digitally and was corrected for changes in the oxygen concentration before each reading.

Forced vital capacity and FEV₁ were measured by instructing the subjects to breathe in to total lung capacity and then perform a forced expiration to residual volume. Subjects unfamiliar with this technique practiced in the sitting position before the study until consistent values were obtained. The maneuver was then undertaken once in each position, allowing the FVC and FEV₁ to be read from the spirometer. Functional residual capacity was mea-

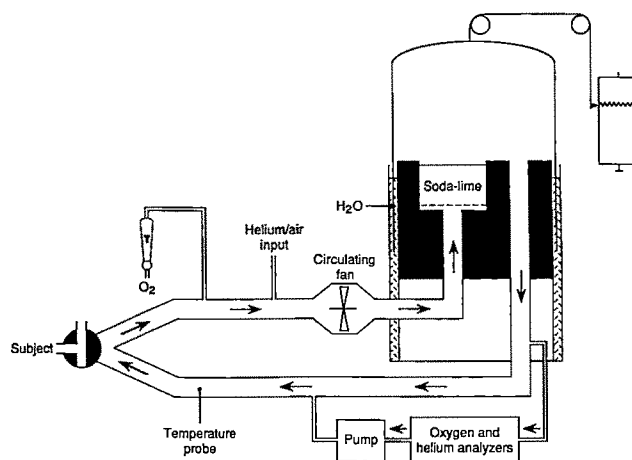


Figure 1. Apparatus used for measurement of FRC.

sured with a closed-circuit helium dilution method (4), all measurements being carried out in 40%–50% oxygen and 8%–12% helium in nitrogen.

Partitioning of ventilation into RC and abdomen-diaphragm components was by respiratory inductive plethysmography (RIP) (5–7). The RIP system consists of two elastic belts approximately 8–10 cm wide placed around the chest and abdomen and secured to the subject using adhesive tape. Each belt contains a zig-zag-patterned single loop of wire through which an alternating current at 1 MHz is passed. Self-inductance of the wire is continuously measured and is proportional to the cross-sectional area within the belt (5). In this study, calibration was by the first stage of the isovolume technique, which is the preferred method when RC partitioning is required (8).

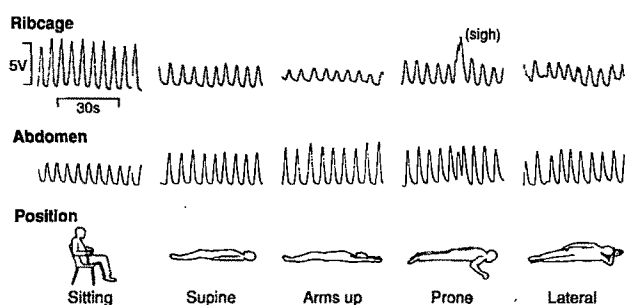


Figure 2. Example of RIP signals in different positions (subject 4).

The RC and abdomen signals are displayed on a paper chart recorder (Figure 2).

Each subject was studied in five positions in random order. These positions were sitting with arms resting on the chair arms, supine with arms by the side, supine with both arms above the head, prone with one arm by the side and one arm in front, and left lateral with the right arm by the side and left arm in front (Figure 2). In each position the following protocol was followed:

1. Calibration of the RIP by the isovolume maneuver
2. "Run-in" period with no mouthpiece until regular respiration returned
3. Recording of RIP signals for 1 min with no mouthpiece, allowing the subjects to breathe via their natural airway
4. Mouthpiece and noseclip applied and a further run-in period allowed while breathing air
5. Recording of RIP signals with mouthpiece/noseclip
6. Subject connected to spirometer and FRC measured
7. A forced vital capacity maneuver performed.

All spirometer volumes were converted to body temperature and pressure saturated, and the average contribution of the RC to tidal volume for each period was calculated as a percentage of total tidal volume (%RC).

Data were analyzed by two-way analysis of variance except for the %RC data, which were pooled for all positions to compare data with and without a mouthpiece/noseclip using a paired *t*-test. Comparisons of %RC between different positions were made using the data obtained without the mouthpiece and noseclip. All comparisons between positions were made in the supine posture, which is the most relevant to anesthetic practice.

Results

Forced vital capacity and FRC for the individual subjects while seated were all within the normal

range (Table 1). There was a significant decrease in FVC when the subject was supine compared with when sitting ($P < 0.001$), individual changes ranging from an increase of 51 mL to a decrease of 645 mL with a mean difference of 300 mL (sd 213). There were no differences in FVC between any of the other postures and supine, nor any significant differences in FEV₁ or FEV₁/FVC% between any positions (Table 2).

Functional residual capacities decreased by a mean value of 806 mL (sd 293) when supine was compared with sitting ($P < 0.001$). Functional residual capacities in the lateral, prone, and arms-up positions were not significantly different from each other, but the mean values of all were significantly greater than in the supine position by approximately 300 mL (mean differences 341 mL (sd 318) when lateral, 351 mL (sd 216) when prone, and 252 mL (sd 329) with arms-up). All were significantly less than the sitting FRC ($P < 0.001$) by approximately 400 mL (Table 2).

In each position %RC was consistently less with a mouthpiece and noseclip but not significantly so for any individual position. When the data were pooled (i.e., 65 pairs of data) there was a significant ($P < 0.05$) decrease of 1.8% in the %RC when breathing changed from the natural airway to a mouthpiece and noseclip. Data for %RC without the mouthpiece showed a highly significant decrease ($P < 0.001$) in the %RC between sitting and supine postures, but no difference between supine and any of the other positions (Figure 2, Table 2).

Discussion

Respiratory inductive plethysmography measures the cross-sectional areas of the chest and abdomen (5) and is now accepted as the most accurate assessment of ventilation available from body surface recordings (6). Respiratory inductive plethysmography has been widely used in respiratory physiology because of its minimal effect on the subject (who usually forgets it is there) and it has also been used as a noninvasive respiratory monitor during sleep studies (7).

The use of a noseclip has no effect on the measurement of FVC and FEV₁ (9). However, use of a mouthpiece and noseclip in another study resulted in an increased tidal volume, decreased respiratory rate, and a slightly increased inspiratory time (10). These respiratory changes were thought to be a result of changing from nasal to oral breathing. We have shown a small but consistent and significant decrease in the RC contribution to tidal volume associated with the use of a mouthpiece and noseclip, but this change is too small to be of practical importance. Regardless of the airway, we have confirmed that breathing is predominantly RC in the sitting position and abdom-

Table 2. Mean Results

Position	FVC (L _{BTPS})	FEV ₁ (L _{BTPS})	FEV ₁ /FVC (%)	FRC (L _{BTPS})	%RC natural	%RC +MP/NC
Sitting	5.01 ± 0.89 ^a	3.79 ± 0.76	77 ± 16	2.91 ± 0.92 ^a	69.7 ± 10.6 ^a	65.1 ± 14.2 ^a
Supine	4.71 ± 0.86	3.70 ± 0.66	79 ± 9	2.10 ± 0.83	32.3 ± 12.0	31.5 ± 10.9
Arms-up	4.59 ± 0.96	3.27 ± 0.80	74 ± 20	2.36 ± 0.76 ^b	33.0 ± 14.7	32.5 ± 12.7
Prone	4.63 ± 1.02	3.49 ± 0.84	76 ± 13	2.45 ± 0.77 ^a	32.6 ± 11.5	32.1 ± 12.1
Lateral	4.87 ± 0.99	3.67 ± 0.71	77 ± 13	2.44 ± 0.75 ^a	36.5 ± 16.8	32.7 ± 15.7

FEV₁, forced expiratory volume in 1 s; FRC, functional residual capacity; FVC, forced vital capacity; %RC, percentage contribution of ribcage to ventilation; MP/NC, mouthpiece and noseclip.

Values are mean ± SD.

Significance of difference relates to the supine position.

^aP < 0.001.

^bP < 0.01.

inal while in the supine position (69.7% RC sitting; 32.3% RC supine). This agrees with the findings of Mannix et al. (2) who also used RIP (60.4% RC sitting; 36.2% RC supine). Sharp et al. (11) used two pairs of magnetometers to measure anteroposterior diameters of chest and abdomen and obtained essentially similar findings (70% RC sitting; 25% RC supine). Vellody et al. (12) used magnetometers to measure both anteroposterior and lateral diameters, from which they calculated cross-sectional areas. Their values for %RC are lower than those of other workers (48% RC sitting; 20% RC supine), and this may be a consequence of assumptions in the calculation of cross-sectional area. Vellody et al. is the only group to have examined partitioning in the prone and lateral positions, and they found larger values for %RC (32%) in these positions compared with the supine position. Thus, our findings agree with their %RC values for prone and lateral positions, but not for supine or sitting.

Our data for FVC and FEV₁ show surprisingly little change with different postures. A slightly increased FVC and unchanged FEV₁ for the sitting position suggest either a greater total lung capacity at the start of expiration or a more complete expiration and hence a lower residual volume, although the latter is unlikely considering the larger FRC when sitting. An increased total lung capacity may result from the subject's arms (and so shoulders) being supported by the chair, thus enhancing the use of the pectorals as accessory respiratory muscles.

This study confirms the well-known change in FRC between upright and supine. Functional residual capacity was almost identical in the prone and lateral positions, being on average 350 mL greater than when supine. Studies using plain radiographs in the lateral position (13,14) have shown that the lower diaphragm is displaced much further cephalad than the upper, which may not move cephalad at all (14). Thus perhaps only the lower diaphragm (in our case the left) contributes to the decrease in FRC, thereby

causing only approximately 50% of the reduction seen from sitting when compared with supine.

Moreno and Lyons (3) found that subjects in the prone position failed to show a significant change in FRC as compared with the supine position, despite a mean change of 149 mL. Rehder et al. (15) used a nitrogen washout technique to measure FRC in 10 volunteers in the prone position, but unfortunately did not compare their data with either the supine or upright postures. They obtained a mean FRC of 3.57 L, which is much larger than that of our subjects even when differences in weight are taken into account (FRC for our subjects, 34 mL/kg; those of Rehder et al., 43 mL/kg). In dogs, the costal part of the diaphragm is less compliant than the crural part (16), but this difference in diaphragmatic morphology has yet to be confirmed in humans. Again, radiographic studies help to explain the changes in FRC when prone. Krayner et al. (17) used CT scanning to reconstruct a three-dimensional image of the diaphragm in three supine and three prone subjects. They observed that two of the three prone subjects still used the posterior part of their diaphragm for ventilation. This, coupled with the possible noncompliant costal diaphragm, may explain the relatively high FRC when prone. In the Rehder et al. study (15), five of the ten volunteers were anesthetized (with paralysis) in the prone position, resulting in a non-significant reduction of 400 mL in their FRC and also a reduction in closing capacity. Similarly, Krayner et al. (17) found a consistent cephalad displacement of the diaphragm during prone anesthesia, which he calculated to represent a mean volume displacement of 615 ± 466 mL. Our data, along with these two studies, indicate that for anesthesia in the prone position, the FRC is initially larger than in the supine position, the reduction in FRC with anesthesia is similar to that seen when supine, and the closing capacity may also be reduced. Thus less disturbance of gas exchange probably will occur during anesthesia in the prone position when compared with su-

pine, but the alveolar to arterial oxygen difference [$\Delta P(A-a)O_2$] during anesthesia in different positions has not been studied.

Many of the most significant studies aimed at explaining the increased $\Delta P(A-a)O_2$ during anesthesia have been performed in CT scanners. Complex changes in diaphragmatic shape have been described (17), and lung opacities have been demonstrated and their extent correlated with the $\Delta P(A-a)O_2$ (1). To perform any chest CT scan, the arms of the subject must be raised above the head to avoid artifacts. We have shown that although this maneuver does not alter the %RC contribution, it does increase FRC by approximately 250 mL, which represents almost half of the usual FRC decrease seen during anesthesia. Once again the effect this position has on closing capacity or the reduction of FRC with anesthesia is unknown. However, if these factors are the same as in the supine arms-down position, then the larger initial FRC may cause studies of anesthesia carried out in CT scanners to underestimate the changes that take place during anesthesia in the normal supine position with the patient's arms by his side.

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Enhanced Potency of Receptor-Selective Opioids After Acute Burn Injury

Brendan S. Silbert, FFARCS, FFARCS, Andrzej W. Lipkowski, PhD,
M. Soledad Cepeda, MD, Stanislaw K. Szyfelbein, MD, Patricia F. Osgood, PhD,
and Daniel B. Carr, MD

Analgesic Peptide Research Unit, Departments of Anesthesia and Medicine (Endocrinology), Massachusetts General Hospital and Shriners Burns Institute, Boston, Massachusetts; Department of Anaesthesia, St. Vincent's Hospital, Melbourne, Australia; Department of Chemistry, Warsaw University, Poland; and Department of Anesthesia, Hospital St. Ignatius, Bogota, Colombia

Dose-response curves of three receptor-selective opioids were established in a group of nonburned and a group of burned rats. Morphine (μ -agonist), buprenorphine (μ - and δ -agonist), and U50488H (κ -agonist) were administered to each group, and analgesia was measured by tail flick latency testing. Each opioid had a significant increase in potency (i.e., a decrease in ED₅₀ values) in the burned (15% body surface area) compared with the nonburned groups. Moderate

doses of each drug (i.e., ED₅₀ doses estimated from nonburned group data) in each case augmented stress-induced analgesia in the burned group. Analgesic doses failed to prevent a significant increase in plasma β -endorphin and corticosterone after larger surface area (25%) burns. Regardless of receptor specificity, opioid analgesic potency is increased acutely after burn injuries.

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Burn injury is a severe form of stress associated with alterations in nociceptive thresholds and hence shares many of the features of stress-induced analgesia described in other settings (1). After a transient interval of stress-induced analgesia, difficult pain problems often emerge; thus, additional studies are indicated to clarify mechanisms of analgesia in this setting. We have previously found distinctive antinociceptive responses between two clinically useful opioids, morphine and butorphanol, given 48 h after acute burn injury in rats and suggested such changes may be related to increased levels of circulating β -endorphin (2). To investigate further the altered response to opioid analgesics after burn injury, we constructed dose-response curves in nonburned rats for three opioid drugs with distinct receptor selectivity and again in another group of rats after acute burn injury. By analyzing changes in analgesic activity for these drugs after acute burn injury, we hoped to identify whether any particular opioid receptor was involved in the changed re-

sponse. Furthermore, because of the extreme pituitary-adrenal activation that contributes to a clinically devastating catabolic state in patients after burn injury, we measured circulating β -endorphin and corticosterone levels in other groups of rats treated with receptor-selective opioids to see if these hormone responses could be modified by analgesic doses of any of these drugs. Receptor selective opioids differentially influence pituitary hormone secretion (3,4).

Methods

Male Sprague-Dawley rats weighing 175-250 g (Taconic Farms, Germantown, N.Y.) were maintained on a 12-h light-dark cycle and allowed free access to food and water. Eighteen rats were used for each dose-response curve. All procedures were approved by the Protocol Review Group of the Subcommittee on Animal Care, Committee on Research, Massachusetts General Hospital.

The day before study, rats were given oxygen and enflurane anesthesia and a Silastic cannula was inserted through the right internal jugular vein into the right atrium and was tunneled to emerge through a small incision at the base of the skull. The protruding stub was occluded with a small metal plug that was easily removable for intravenous drug administration

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Address correspondence to Dr. Carr, Department of Anesthesia, Massachusetts General Hospital, Boston, MA 02114.

and blood sampling. After the rats were prepared, they were housed individually in cages overnight.

Rats were divided into nonburned (NB) and burned (B) groups. All rats were anesthetized with enflurane in oxygen, after which only the B group had ventral and dorsal areas shaved, and a limited portion of each surface was immersed for 10 s in water at 100°C. The body surface area (BSA) and % burn area were calculated from the following equations:

$$\text{BSA (m}^2\text{)} = 0.0011 \times \text{weight (g)} \times 0.63,$$

$$\% \text{BSA burned} = \frac{\text{burned area (m}^2\text{)}}{\text{BSA (m}^2\text{)}} \times 100.$$

In the B group of rats tested for analgesic potency, BSA was limited to approximately 15%, whereas a larger area (25%) was chosen for stress-hormone studies on the basis of prior results indicating that this was the lowest %BSA consistently able to evoke a maximal pituitary-adrenal response (1). Because our previous studies had demonstrated an acute endogenous analgesic response after comparable full-thickness burns (1) and because our (5) and other observations indicate that pain intensity is modest as long as the injured clinical site is not manipulated, no analgesics were deemed necessary after inhaled anesthesia.

At the conclusion of the study, animals were killed using volatile anesthetic (ether).

Three drugs were administered intravenously. Morphine, a predominantly μ -agonist; buprenorphine, a predominantly μ - and δ -agonist peptide (6,7); and U50,488H, a predominantly κ -agonist (8). The drugs were dissolved in saline solution, injected into the previously implanted cannulas using a 1-mL syringe, and flushed with saline solution. Eighteen rats were used for each drug in both NB and B groups. The doses used were as follows: morphine: 1, 2, and 5 $\mu\text{mol/kg}$ (NB group) and 1, 2, 3, and 5 $\mu\text{mol/kg}$ (B group); buprenorphine: 5, 10, and 15 $\mu\text{mol/kg}$ (NB group) and 5, 7.5, and 10 $\mu\text{mol/kg}$ (B group); U50,488H: 5, 10, and 15 mg/kg (NB group) and 2.5, 5, 10, and 15 mg/kg (B group). An additional six rats in the B group were given no drug to quantitate stress-induced analgesia resulting from the burn itself.

Analgesia was measured by the tail flick latency test (9) performed by gently restraining the rat with a cloth and placing the tail under a radiant heat source that was activated simultaneously with a timer. When the rat flicked the tail aside, a photocell was uncovered turning off both the heat source and the timer thus recording tail flick latency. Five trials at 1-min intervals with a maximum exposure to heat (cut off) of 7 s were performed. Light intensity was adjusted to give a baseline tail flick latency of 3-4 s.

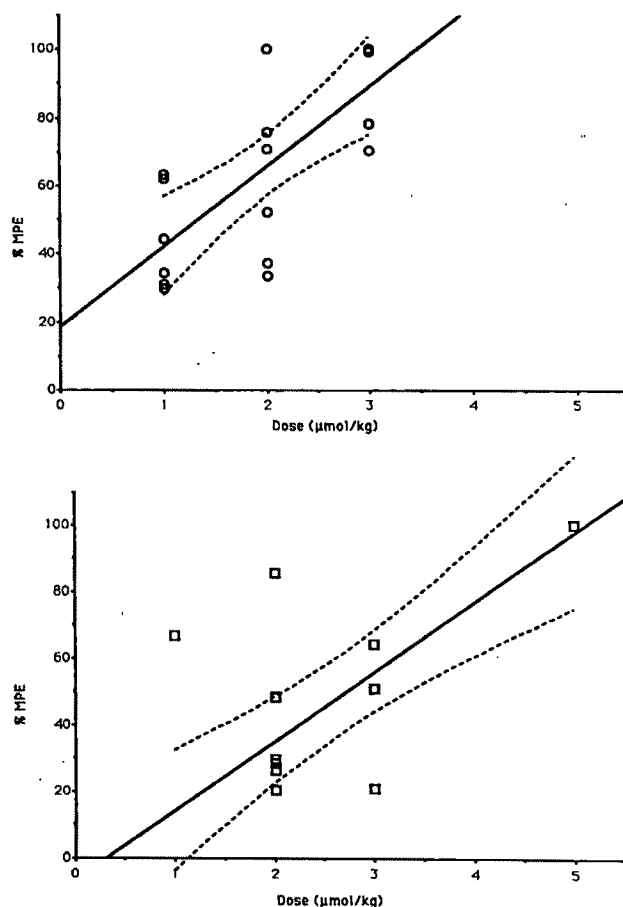


Figure 1. Dose-response curves for groups of burned (\circ) (above) and nonburned (\square) rats (below). Eighteen rats were used in each group. Rats were given intravenous morphine and analgesia tested by tail flick. %MPE is the percent maximum possible effect. 95% confidence limits are shown (dotted lines).

The degree of analgesia was expressed as a percentage of maximum possible effect (MPE) calculated as

$$\% \text{ MPE} = \frac{(\text{posttreatment latency} - \text{control})}{\text{cut-off latency} - \text{control}} \times 100.$$

In the NB group, the MPE was measured for each dose of each drug at baseline, 15, 30, and 60 min after administration of that drug and then at hourly intervals. In the B group, the baseline measurements were taken before the burn injury and at 60, 75, 90, and 120 min after the burn, and then hourly. In this group, the rats receiving drugs were given the drug intravenously after the 60-min measurement. The largest value for each dose of each drug in each group was used to establish a dose-response curve.

To examine a possible effect of analgesic drugs on plasma levels of the stress hormones β -endorphin and corticosterone, five rats were allocated to each of

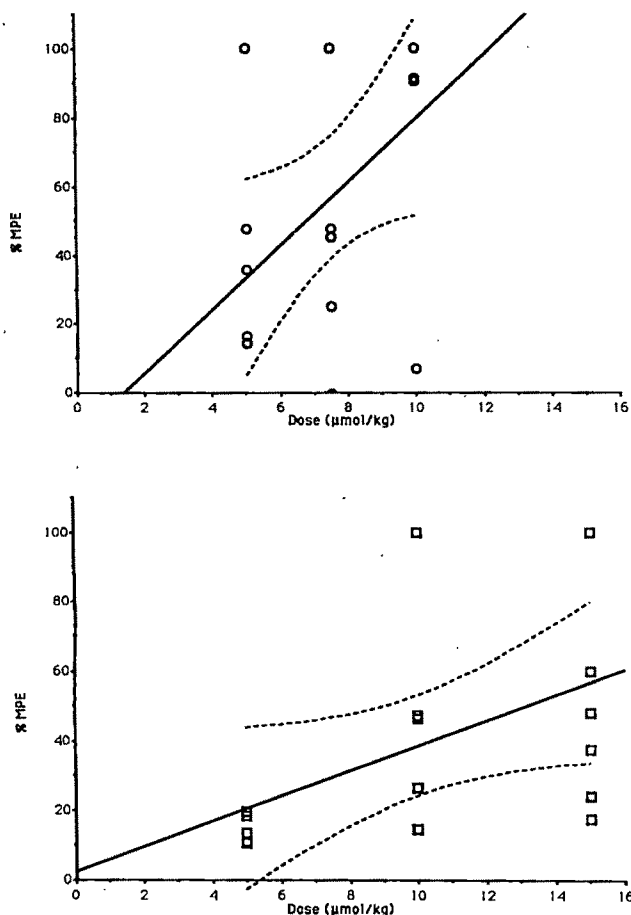


Figure 2. Dose-response curves for groups of burned (○) (above) and nonburned (□) rats (below). Eighteen rats were used in each group. Rats were given intravenous buphalin and analgesia tested by tail flick. %MPE is the percent maximum possible effect. 95% confidence limits are shown (dotted lines).

the following treatment groups: (a) no drug, (b) 4 $\mu\text{mol/kg}$ of intravenous morphine, (c) 20 $\mu\text{mol/kg}$ of intravenous buphalin, and (d) 15 mg/kg of intravenous U50,488H. These dosages were in excess of the ED_{50} values for tail flick latency determined in pilot dosage studies on nonburned rats. Drugs were given to the rats 15 min before an $\sim 25\%$ BSA burn was administered to the rats to elicit a maximal hormonal response (1). Blood samples (1 mL) were drawn, centrifuged with edetic acid (50 μL of an 18% solution), and the plasma was removed using a pipette. The red cells were returned after having been diluted in normal saline solution to equal the original volume. Samples were taken before burning and at 1 and 2 h after burning. The plasma samples were rapidly frozen and stored at -20°C for later analysis of β -endorphin and corticosterone. Plasma immunoreactive β -endorphin (10) and corticosterone (Cambridge Medical Diagnostics, Billerica, Mass.) were

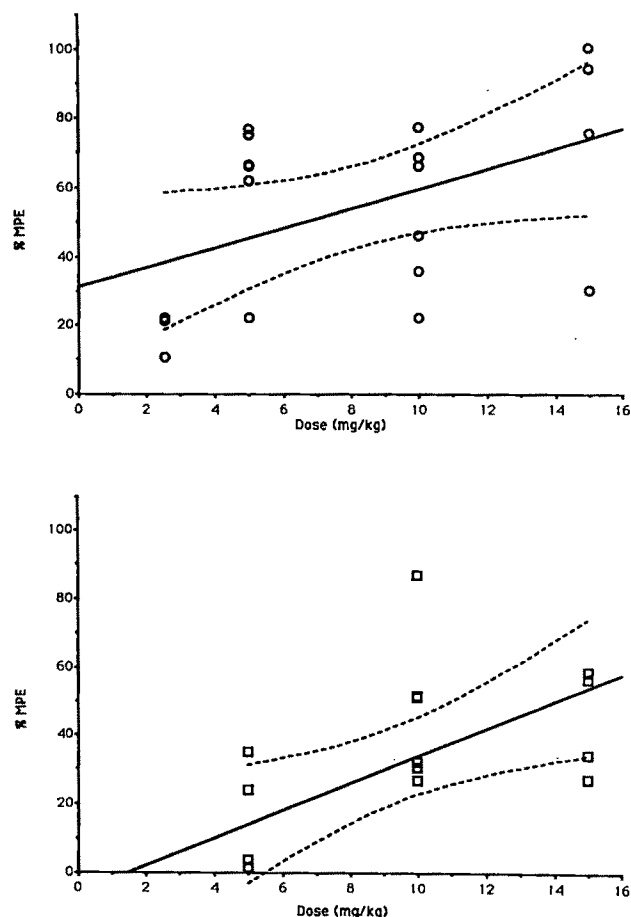


Figure 3. Dose-response curves for groups of burned (○) (above) and nonburned (□) rats (below). Eighteen rats were used in each group. Rats were given intravenous U50,488H and analgesia tested by tail flick. %MPE is the percent maximum possible effect. 95% confidence limits are shown (dotted lines).

assayed by published methods. Cut-off levels of 2000 pg/mL and 500 mg/mL were used for β -endorphin and corticosterone, respectively, because higher values were imprecise in the assay conditions used (11).

The dose-response curves were prepared by linear regression of %MPE versus drug dose using Statview (Abacus Concepts Inc., Berkeley, Calif.). Using Minitab (Minitab Inc., State College, Pa.), the ED_{50} values and 95% confidence limits were derived from the linear regression lines as the drug dosage corresponding to %MPE = 50%. Unpaired t -tests were used to compare ED_{50} values. Analysis of variance was carried out using Superanova (Abacus Concepts). The level of significance was $P < 0.05$.

Results

Non-drug-treated rats had no behavioral evidence of nociception (e.g., writhing, vocalizing, licking, motor

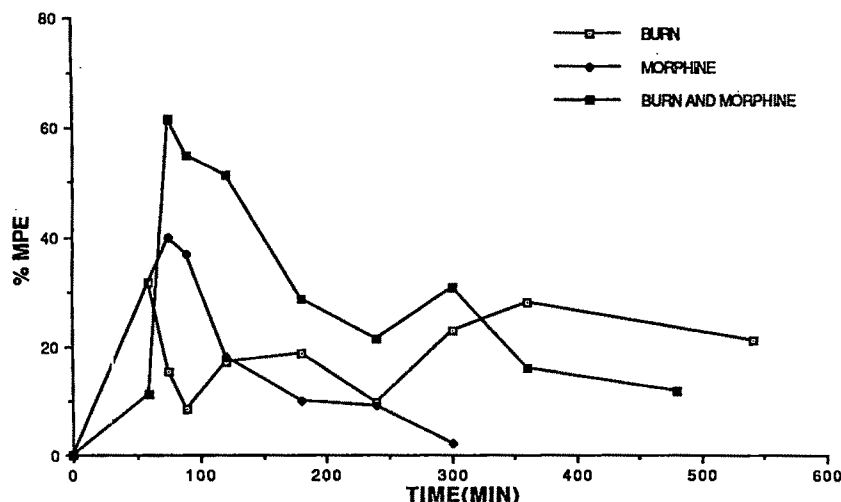


Figure 4. Time effect curves for analgesia after burn alone, after treatment with 2 μ mol/kg of morphine alone, and after treatment with 2 μ mol/kg of morphine following burn. %MPE is the percent maximum possible effect.

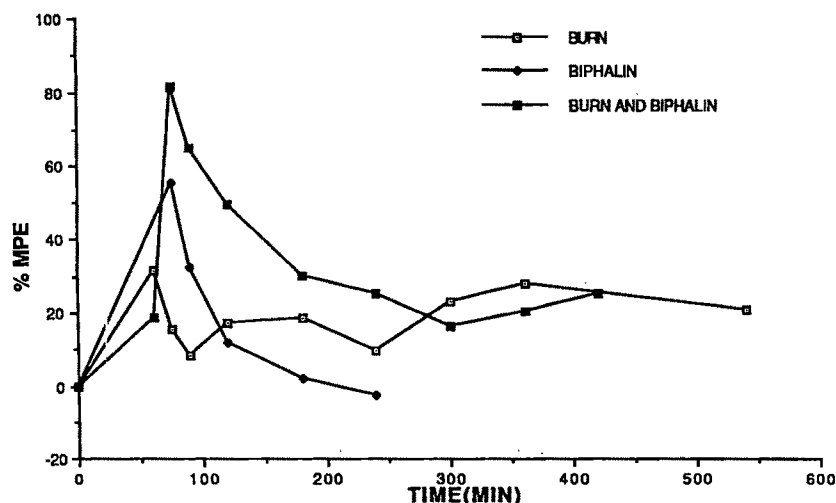


Figure 5. Time effect curves for analgesia after burn alone, after treatment with 10 μ mol/kg of biphalin alone, and after treatment with 10 μ mol/kg of biphalin following burn. %MPE is the percent maximum possible effect.

activity), as expected for these acute studies. Indeed, endogenous analgesia was evidenced by elevations of tail flick latency responses in the non-drug-treated B group animals.

For tail flick latency, the dose-response curves with 95% confidence limits for morphine, biphalin, and U50,488H in burned rats and in nonburned rats are shown in Figures 1–3. In all cases, the dose-response curves of the B group are shifted to the left from that of the NB group. The respective ED₅₀ (95% confidence limits) for tail flick latencies in the B and NB groups are morphine, 1.63 (1.29–1.97) and 2.63 (2.21–3.16) μ mol/kg; biphalin, 7.34 (6.37–8.30) and 10.69 (8.66–12.73) μ mol/kg; U50,488H, 7.93 (5.92–9.96) and 11.12 (8.92–13.11) mg/kg.

The stress-induced analgesic effect of burn alone can be seen in Figures 4–6. The % MPE for tail flick latency in the non-drug-treated rats in the B group is

plotted against time together with responses in burned and nonburned rats given a single dose of each drug (ED₅₀ in pilot dosage studies in nonburned rats). The combination of the burn and each opioid produced significantly greater analgesia than the burn alone for each of the three opioids (Games-Howell post-hoc tests). Two-way analysis of variance for repeated measures did not show a significant difference between the analgesia produced by the burn alone and either 2 μ mol/kg of morphine ($P = 0.15$) or 10 μ mol/kg of biphalin ($P = 0.065$). However, the analgesia produced by 10 mg/kg of U50,488H was significantly greater than that produced by the burn alone ($P = 0.01$).

The levels of stress hormones in the rats subjected to the larger BSA burns are shown in Figures 7 and 8. A two-way analysis of variance for repeated measures showed a significant increase in levels of both

Figure 6. Time effect curves for analgesia after burn alone, after treatment with 10 mg/kg of U50,488H alone, and after treatment with 10 mg/kg U50,488H following burn. %MPE is the percent maximum possible effect.

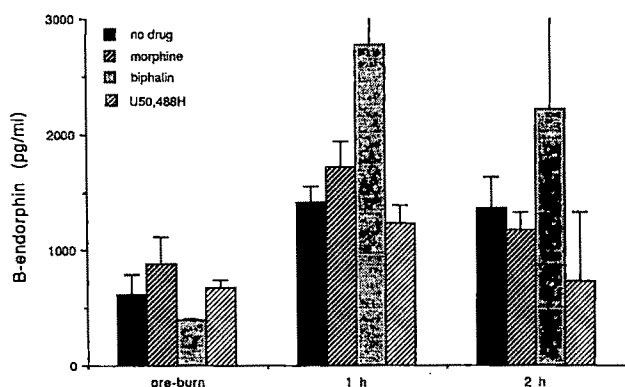
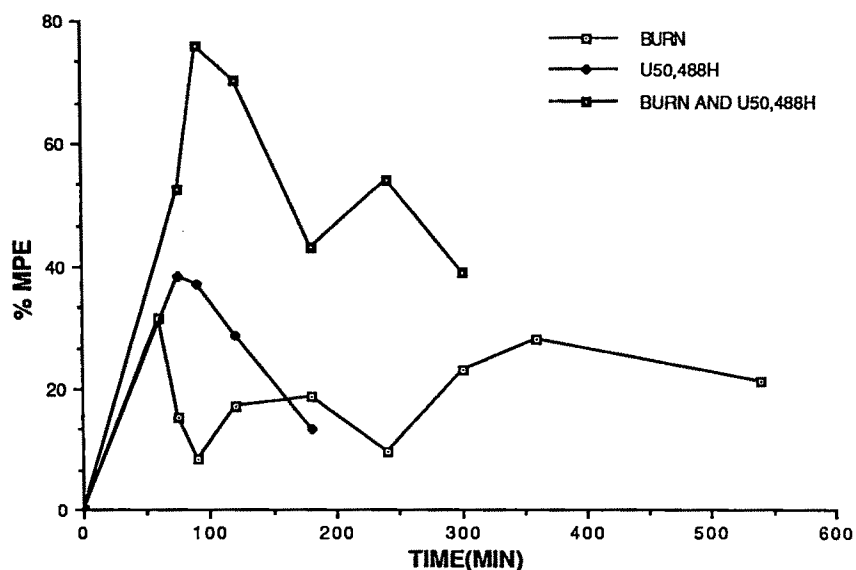


Figure 7. β -Endorphin levels before and at 1 and 2 h after burn. Error bars represent the standard error of the mean.

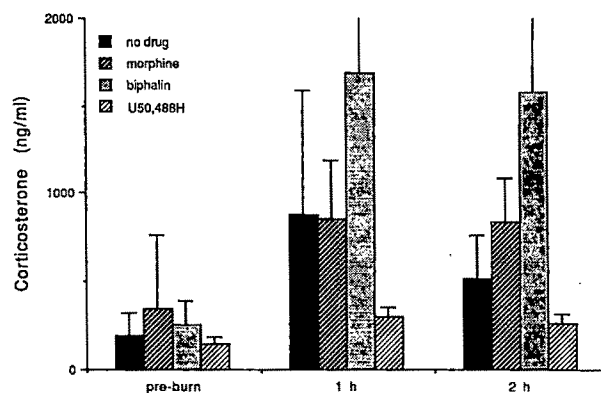


Figure 8. Corticosterone levels before and at 1 and 2 h after burn. Error bars represent the standard error of the mean.

β -endorphin and corticosterone after burn at both 1 and 2 h ($P = 0.003$ and $P = 0.0001$, respectively: Games-Howell post-hoc test). None of the intravenous analgesic doses of the three study drugs significantly altered this response for levels of β -endorphin ($P = 0.102$). There was a significant effect due to drug treatment for the levels of corticosterone ($P = 0.0001$). Post-hoc testing (Games-Howell) showed this was mainly due to variation between the different drugs. Biphalin alone produced a significant increase in corticosterone above that in the non-drug-treated group.

Discussion

In clinical practice, there is a large variation in an individual's response to a given dose of an opioid. Variations in serum concentrations up to fourfold to

produce adequate pain relief have been observed for meperidine analgesia (12). Pharmacokinetic reasons such as differing rates of absorption and volume of distribution may play a part. However, pharmacodynamic factors, such as differing opioid receptor subtype populations or interactions with circulating or locally released endogenous opioids, may account, at least in part, for the wide variability in response. We sought to explore the pharmacodynamic basis for variability in response by using different receptor-selective opioids in a rat burn model.

Despite the fact that morphine, biphalin, and U50,488H have differing receptor affinities (7,13), all the ED_{50} values after 15% BSA burns decreased for tail flick latency. The analgesic potency of the κ -agonist butorphanol is enhanced at 2 days after burn injury (2). Our present results indicate that such enhancement of analgesic potency occurs early (within 75 min after burn) and is not limited to κ -agonists.

The presence of the burn itself provides a level of analgesia. Similar analgesia is activated by many stressors and environmental changes in experimental animals (14,15). The stress-induced analgesia of the burn injury may share many properties with other forms of stress-induced analgesia including antagonism by naltrexone and may be opioid in character. This may be due to an increase in circulating corticosterone and β -endorphin (11,16), given recent findings that opioids may possess a local analgesic action in the periphery. Opioids produce antinociception in inflammation-related pain by acting at peripheral sites (17,18). In the central compartment, i.e., the spinal cord, gene activation of *fos* and opioid genes occurs early after injury or inflammation (19) and is modified by opioid analgesia (20). In preliminary studies, we have found that thermal injury may alter opioid gene expression in the rat spinal cord (21).

Whatever the mechanism, stress-induced analgesia due to the burn may be an important factor in adding to the potency of each of the three analgesics after burn injury. As can be seen from Figures 4-6, some additive effect of the burn and the analgesic seems apparent for each of the three drugs tested, regardless of receptor selectivity. Both β -endorphin and corticosterone increase after burn injury in excess of 20% BSA (1). Opioid analgesia is often associated with an attenuation in the amounts of these hormones released (22), although Kehlet (23) and others have reported persistent systemic hormonal responses postoperatively during opioid analgesia. Nonetheless, the increase in corticosterone and β -endorphin after the burn was unaltered by the administration of any of the three receptor-selective drugs. Although the pituitary-adrenal axis has been viewed as under exclusive central nervous system control (24), we have shown that the release of both β -endorphin and corticosterone may reflect peripheral stimuli in the absence of central nervous system connections after burn injury (13). This may well explain the continued elevation of these stress hormones despite pretreatment with analgesics.

One could speculate that the persistent elevation in circulating stress hormones may account for the analgesic potentiation of the three receptor-selective drugs, or that this potentiation was derived from a drug effect on central neural pathways mobilized during stress, or that simultaneous drug actions in the central or peripheral compartments underlay our results. On the other hand, the increased potency appeared to play no part in diminishing the release of stress hormones.

In conclusion, enhanced analgesic potency after burn injury tends to augment stress-induced analgesia and is relatively independent of receptor selectivity. The release of β -endorphin and corticos-

terone is not prevented by the prior administration of analgesic doses of opioids and may play a part in the enhanced potency of analgesics that follows acutely after burn injury.

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Adverse Interaction Between Bupivacaine and Halothane on Ventricular Contractile Force and Intraventricular Conduction in the Dog

Lucien Bertrix, MD, PhD, Quadiri Timour, PhD, Richard I. Mazze, MD, Marc Freysz, MD, Kamran Samii, MD, and Georges Faucon, MD, PhD

Claude Bernard University, Lyon; University of Dijon; and University of Paris (Sud), Kremlin-Bicetre, France; Stanford University, Stanford; and Veterans Administration Medical Center, Palo Alto, California

Regional anesthesia with bupivacaine in pediatric patients is often accompanied by light levels of halothane general anesthesia. To determine the potential cardiotoxicity of these two drugs when used together, we defined the interaction between moderate plasma bupivacaine concentrations (1270–1760 ng/mL) and halothane (end-tidal concentrations, 0.5%–1.0%) on ventricular contractility and conduction in 22 closed-chest dogs anesthetized with chloralose. Bupivacaine alone (1-mg/kg intravenous bolus plus a 0.1-mg·kg⁻¹·min⁻¹ constant rate infusion) resulted in significant increases in ventricular conduction time (VCT) and effective refractory period (VERP) and nonsignificant decreases in dP/dt_{max} and

blood pressure. The addition of halothane resulted in hypotension and in progressively increasing plasma bupivacaine levels secondary to reduced hepatic clearance, which led to further dose-related significant increases in VCT and VERP and to significant decreases in dP/dt_{max} and blood pressure. In other dogs given halothane but in which bupivacaine levels were held constant (1400 ng/mL), VCT remained constant and VERP lengthened slightly, whereas dP/dt_{max} decreased. We conclude that the combination of bupivacaine and halothane can cause adverse effects on ventricular contractility and intraventricular conduction.

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Although bupivacaine (1–6) and halothane (7–12) are negative inotropes, the separate administration of each is rarely accompanied by serious abnormalities in cardiac function. However, these drugs are often used together in pediatric anesthetic practice when light levels of halothane general anesthesia are administered to facilitate administration of the regional block and to produce hypnosis and additional analgesia during the surgical procedure (13–15). Thus, there is a potential for the cardiotoxic interaction of these two agents. In the present study, we examined the question of whether the concurrent administration of both drugs would be associated with depression of ventricular contractile force owing to the synergism of their negative inotropic effects. Another concern was that both experimentally in the laboratory and in clinical practice,

bupivacaine has been reported to cause ventricular conduction disorders with reentrant arrhythmias; occasionally, these have had a fatal outcome (3,4,16–19). Although halothane does not have an appreciable influence on intraventricular conduction (20–22), we wanted to determine whether its administration would enhance bupivacaine-induced rhythm disorders. Thus, a second goal of the study was to determine the effects of bupivacaine combined with halothane on ventricular conductivity.

Methods

Animal Preparation

After approval of the protocol was obtained from the institutional animal care committee, we initially randomly allocated 16 mongrel dogs of either sex, weighing 16–24 kg, to treatment with either bupivacaine-halothane (group 1, *n* = 10) or halothane alone (group 2, control; *n* = 6). Later, as a consequence of our analysis of data from group 1 dogs in which we observed progressively increasing bupivacaine concentrations as halothane concentrations were in-

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Address correspondence to Dr. Mazze, (11PA), VA Medical Center, 3801 Miranda Avenue, Palo Alto, CA 94304. Address reprint requests to Dr. Bertrix, Claude Bernard University, Rockefeller Avenue, F-69008, Lyon, France.

creased, we studied a third group of six dogs treated in the same fashion as the first group, except that the rate of bupivacaine infusion was decreased from $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to 0.08, 0.06, and $0.04 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ as halothane concentrations were increased from 0.0% to 0.5%, 0.7%, and 1.0%, respectively.

Food was withheld the night before the study, but water was available ad libitum. Anesthesia was induced with an intravenous injection of chloralose (80 mg/kg). After intubation of the trachea, the lungs were ventilated with a Bird Mark VIII respirator delivering an air-oxygen mixture (40% and 60%, respectively). The arterial blood gas tensions and pH were checked approximately every 15 min, and values were maintained in the normal range by modifying ventilator settings. The body temperature was carefully monitored with an electronic esophageal thermometer and was kept constant at 39°C by means of an infrared heater placed at a variable distance from the animal, as a reduction in core temperature from 39° to 35°C further impairs the ventricular conduction deficit caused by bupivacaine (23).

Measurements

A surface electrocardiogram was obtained using needle electrodes introduced under the skin of each leg and connected to an Elema-Schonander electrocardiograph. The cardiac electrical activity was continuously monitored on a Siemens EM 531 oscilloscope. The mean arterial blood pressure (MAP) was measured directly using a catheter inserted percutaneously into the left femoral artery and connected to a Statham transducer and a Narcotrace 80 polygraph. The right femoral artery was cannulated, and a 6F argon catheter was positioned in the left ventricle to measure pressure. Waveforms were displayed on a Thomson Medical Telco oscilloscope, and dP/dt was electronically derived from the intraventricular pressure signal and recorded on a Narcotrace 80 polygraph. Left ventricular $\text{dP/dt}_{\text{max}}$ ($\text{LV dP/dt}_{\text{max}}$) was taken as the peak positive deflection of the dP/dt trace. To assess the effects of treatment on ventricular contractility independent of the indirect influence of variations in heart rate, a 6F Plastimed Elecath pacing electrode was introduced percutaneously into the right jugular vein and was advanced centrally to the base of the right ventricle just beneath the tricuspid valve. The electrode was connected to a Hugo Sachs stimulator that delivered square-wave stimuli (S1) of 1.5 mA (approximately three times the threshold intensity) and 5-ms duration at a rate of 180 beats/min. Measurements also were made with the heart beating spontaneously.

Right ventricular conduction time (VCT) was measured using a 6F Plastimed USCI bipolar recording

electrode introduced percutaneously into the right femoral vein and advanced to the apex of the right ventricle. This electrode was connected to an Elema-Schonander electrocardiograph lead designed to record His bundle potentials. Ventricular conduction time was defined as the time that elapsed between stimulation by the pacing electrode and the onset of electrical activity recorded at the apex. In a similar manner, QRS duration was measured during sinus rhythm.

The stimulating electrode also was used for determination of the effective refractory period in ventricular muscle (VERP) using the extrastimulus method (24). In brief, while the ventricles were driven by the stimuli S1 (described previously), a premature extrastimulus, S2, of the same characteristics was introduced. The longest coupling interval, S1-S2, at which S2 just failed to capture was taken as the VERP. To avoid artifacts owing to changes of average rate produced by the extrastimuli, care was taken not to initiate S2 before 8–10 S1 stimuli.

Experimental Protocol

Group 1 dogs received a 1-mg/kg intravenous loading dose of preservative-free bupivacaine hydrochloride (Marcaine Roger Bellon), followed by an intravenous infusion of bupivacaine at a rate of $0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ throughout the experiment. The loading dose and the infusion rate were chosen to result in arterial blood bupivacaine concentrations between 1200 and 1800 ng/mL, values that correspond to the peak concentrations generally observed after regional anesthesia. Thirty minutes after the loading dose had been administered and the infusion started, steady-state control measurements ($\text{LV dP/dt}_{\text{max}}$, VCT, and VERP) were made. Halothane then was administered with a Fluotec Mark III vaporizer in quantities sufficient to maintain end-tidal concentrations of 0.5%, 0.7%, and 1.0%. These were measured with a Datex Capnomac (together with carbon dioxide levels). When steady anesthetic concentrations had been maintained for 15 min, measurements again were made.

Experiments on group 2 dogs were conducted in an identical manner and time frame except that bupivacaine was not administered (i.e., 30 min after the monitors were placed, the three concentrations of halothane were administered and hemodynamic and electrophysiologic measurements were made). The protocol for group 3 dogs was the same as for group 1, except that the rate of bupivacaine infusion was progressively decreased as the concentration of halothane was increased to keep arterial bupivacaine concentrations relatively constant.

Arterial blood bupivacaine levels were determined

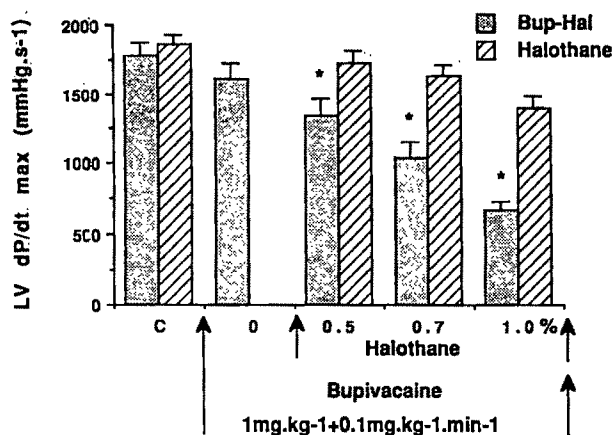


Figure 1. A comparison of left ventricular dP/dt_{max} (LV dP/dt_{max}) during pacing at 180 beats/min under the influence of bupivacaine plus halothane (group 1, $n = 10$) and halothane alone (group 2, $n = 6$). Significant differences between the groups were noted at all halothane concentrations. Intergroup comparisons were made with unpaired Student's t -test. Mean values \pm SE are shown. * $P < 0.05$ is considered statistically significant.

using a high-performance liquid chromatography method, with a limit of sensitivity of 20 ng/mL (25). Samples were obtained each time hemodynamic and electrophysiologic measurements were made.

Statistics

Data were analyzed using two-way (group and halothane concentration) repeated measures analysis of variance and Scheffe's test when significant differences were found with analysis of variance. When appropriate, unpaired Student's t -tests also were used. $P < 0.05$ was considered statistically significant. Values are presented as the mean \pm SE.

Results

Treatments were started only after a steady state had been achieved, i.e., two control measurements (5 min apart) during ventricular pacing at 180 beats/min of LV dP/dt_{max} and VCT that did not vary by more than 10%.

Constant Rate of Bupivacaine Infusion Plus Halothane (Group 1)

The administration of bupivacaine during ventricular pacing at 180 beats/min resulted in a slight, statistically insignificant decrease in LV dP/dt_{max} from 1785 ± 91 to 1615 ± 109 mm Hg/s (Figure 1). The addition of 0.5% halothane resulted in a further decrease to 1340 ± 125 mm Hg/s, which was statistically significant ($P < 0.05$); administration of 0.7%

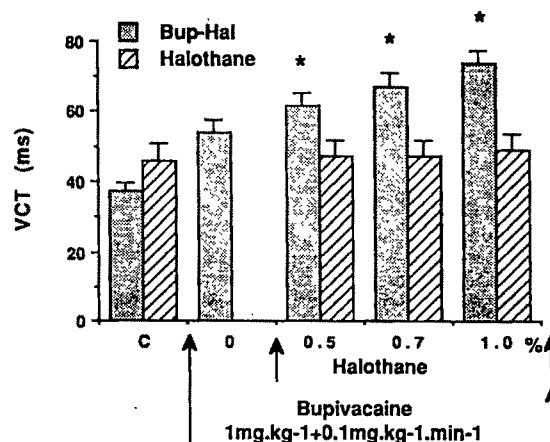


Figure 2. A comparison of ventricular conduction time (VCT) during pacing at 180 beats/min under the influence of bupivacaine plus halothane (group 1) and halothane alone (group 2). Significant differences between the groups were noted at all halothane concentrations. Mean values \pm SE are shown. * $P < 0.05$ is considered significant.

and 1.0% halothane caused additional reductions to 1030 ± 123 and 670 ± 62 mm Hg/s, respectively ($P < 0.05$). In the absence of pacing, decreases in LV dP/dt_{max} were similar to those that occurred during pacing; the variations in heart rate remained moderate, but all values were somewhat higher: control, 2265 ± 106 mm Hg/s; after bupivacaine infusion, 2115 ± 137 mm Hg/s (not significant); and after 0.5%–1.0% halothane, 1855 ± 148 to 1415 ± 135 mm Hg/s ($P < 0.05$).

The effects of the bupivacaine-halothane combination on cardiac electrophysiologic phenomena were qualitatively similar but quantitatively different from those on contractility. Ventricular conduction time was significantly prolonged after administration of bupivacaine alone (38 ± 2 to 54 ± 4 ms) but the additional lengthening that followed administration of halothane was significant only at the 1.0% concentration (74 ± 4 ms, Figure 2). The effects of bupivacaine-halothane on QRS duration were similar to those on VCT noted previously, i.e., significant lengthening caused by bupivacaine alone (62 ± 1 to 79 ± 2 ms) with further significant lengthening (to 98 ± 5 ms) only at the 1.0% concentration (Figure 3). Bupivacaine treatment resulted in a significant prolongation of VERP (147 ± 4 to 161 ± 4 ms) that was not further increased by the addition of halothane (Figure 4).

The administration of bupivacaine had no effect on MAP (143 ± 6 to 142 ± 9 mm Hg), whereas the addition of halothane caused dose-related decreases in MAP from 125 ± 10 mm Hg at 0.5% to 78 ± 7 mm Hg at 1.0% ($P < 0.05$, Figure 5). Decreases in heart rate secondary to bupivacaine alone and to the

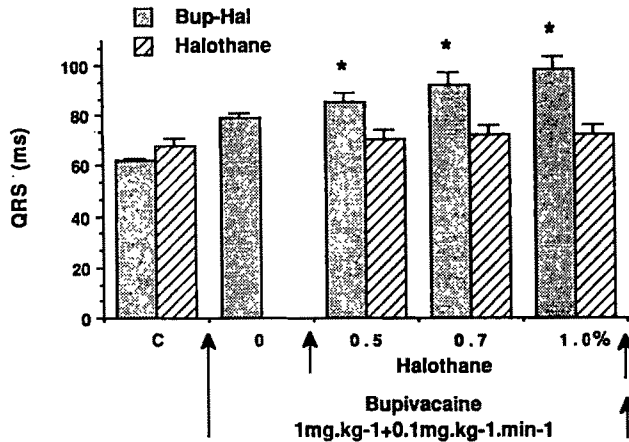


Figure 3. A comparison of QRS duration under the influence of bupivacaine plus halothane (group 1) and halothane alone (group 2). Significant differences between the groups were noted at all halothane concentrations. Mean values \pm SE are shown. * $P < 0.05$ is considered significant.

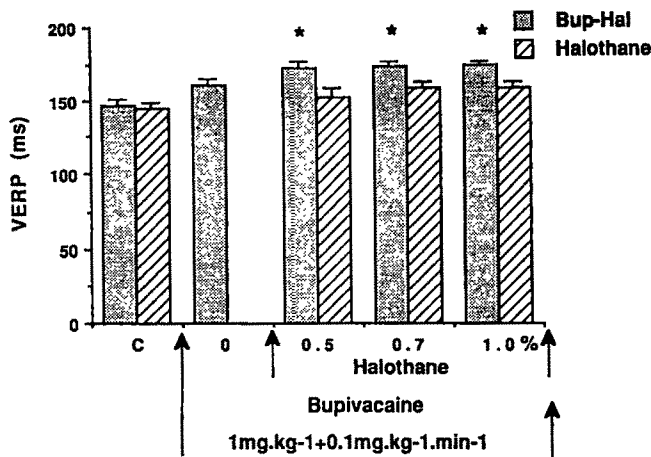


Figure 4. A comparison of ventricular effective refractory period (VERP) during pacing at 180 beats/min under the influence of bupivacaine plus halothane (group 1) and halothane alone (group 2). Significant differences between the groups were noted at all halothane concentrations. Mean values \pm SE are shown. * $P < 0.05$ is considered significant.

bupivacaine-halothane combinations were not statistically significant (data not shown).

Bupivacaine concentration in arterial blood plasma increased significantly from 1270 ± 80 ng/mL before halothane administration to 1760 ± 100 ng/mL at the 1.0% concentration (Figure 6). In the absence of halothane, bupivacaine levels remained stable.

Halothane Alone (Group 2)

Halothane significantly depressed myocardial contractility: during pacing LV dP/dt_{max} gradually declined from 1867 ± 70 mm Hg/s (control) to $1400 \pm$

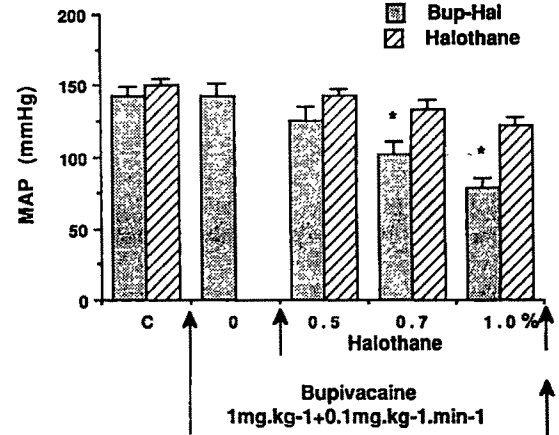


Figure 5. A comparison of mean arterial pressure (MAP) during pacing at 180 beats/min under the influence of bupivacaine plus halothane (group 1) and halothane alone (group 2). Significant differences between the groups were noted at 0.7% and 1.0% halothane. Mean values \pm SE are shown. * $P < 0.05$ is considered significant.

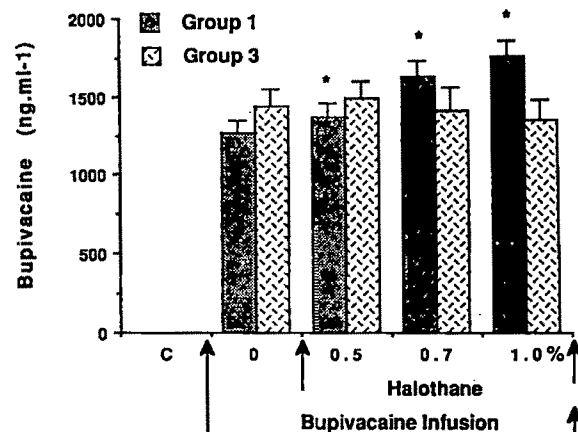


Figure 6. Plasma bupivacaine concentrations in group 1 dogs ($n = 10$) treated with a bolus (1 mg/kg) plus an infusion of bupivacaine administered at a constant rate ($0.1 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) and group 3 dogs ($n = 6$) treated with a bolus of bupivacaine (1 mg/kg) plus an infusion administered at a decreasing rate as halothane concentrations were increased. There was a significant increase in bupivacaine concentrations in group 1 dogs with each successive halothane concentration; bupivacaine concentrations in group 3 dogs remained stable. Mean values \pm SE are shown. * $P < 0.05$ is considered significant.

84 mm Hg/s (1.0%); while the heart was beating spontaneously, LV dP/dt_{max} decreased from 2100 ± 84 mm Hg/s (control) to 1517 ± 102 mm Hg/s (1.0%). The decreases at all halothane concentrations were significant. However, unlike the results in group 1, changes in conduction did not parallel changes in contractile force: VCT and QRS duration remained nearly stable throughout halothane administration. Similarly, there was a moderate increase in VERP from 145 ± 4 to 158 ± 5 ms, which was significant at the 0.5% and 0.7% concentrations ($P < 0.05$).

Halothane caused a dose-related slowing of the sinus rate from 140 ± 12 to 118 ± 7 beats/min, with statistical significance achieved only at the 1% concentration. Mean arterial blood pressure was also reduced in a dose-related fashion from 150 ± 4 to 121 ± 6 mm Hg; but, again, statistical significance was achieved only at the 1% concentration (Figure 5).

Comparison Between Group 1 and Group 2 Dogs

During pacing, the combination of bupivacaine-halothane depressed LV dP/dt_{\max} more than did halothane alone, with the difference between the two groups being significant at each halothane concentration (Figure 1). Interestingly, bupivacaine-induced impairment of VCT became worse when halothane was added, even though treatment with halothane alone was virtually devoid of any effect on ventricular conduction. The differences between the two groups in VCT (Figure 2) as well as in QRS duration (Figure 3) were significant at all halothane concentrations. With minor variations, VERP also was more influenced by the combination of bupivacaine-halothane than by halothane alone (Figure 4).

The decrease in MAP was greater with combined treatment than with halothane alone; the difference first achieved statistical significance at a halothane concentration of 0.7% (Figure 5). On the contrary, the difference in sinus rate between the groups never achieved statistical significance.

Decreasing Rate of Bupivacaine Infusion Plus Halothane (Group 3)

Progressively decreasing the rate of bupivacaine infusion during halothane administration resulted in relatively constant bupivacaine levels throughout the experiment (Figure 6). Under these conditions, QRS duration and VCT, initially lengthened by bupivacaine from 58 ± 4 to 74 ± 5 ms and from 42 ± 4 to 58 ± 6 ms, respectively, did not further increase (76 ± 7 and 63 ± 5 ms) even at the highest halothane concentration. Changes in VERP and LV dP/dt_{\max} were different: VERP increased whereas LV dP/dt_{\max} decreased significantly as the concentration of halothane was increased from 0.0% (from 138 ± 2 to 156 ± 2 ms) to 1.0% (from 1780 ± 98 to 1162 ± 76 mm Hg/s) during pacing. Thus, the combination of bupivacaine and halothane results in greater depressant effects on myocardial refractoriness and on contractility than does either drug alone even in the absence of hypotension and of increasing bupivacaine levels. In contrast, when bupivacaine levels are artificially maintained constant, intraventricular conduction disorders caused by bupivacaine are no longer aggravated by the administration of halothane.

Discussion

In the present study, a bolus dose of 1 mg/kg of bupivacaine, followed by an infusion of 3 mg/kg over 30 min (i.e., a total dose of 4 mg/kg or about twice the usual amount recommended for regional anesthesia) produced insignificant reductions in ventricular contractile force and hemodynamics. This is in contrast to the cardiotoxic effects reported to result from higher bupivacaine doses (1,3-5). Halothane in usual clinical concentrations lowered LV dP/dt_{\max} as well as MAP, confirming its well-known negative inotropic properties (7-12), although this degree of depression probably is of no clinical consequence. The cardiac depressant effect of halothane was probably due to decreased ventricular filling secondary to the effect of halothane on the sympathetic nervous system.

In contrast to the rather benign effects of bupivacaine and halothane when administered separately, they caused significant cardiac depression and conduction disturbances when administered together (group 1). The depressant effects of the combination were attenuated to some extent by their bradycardiac effect as myocardial contractile force assessed by LV dP/dt_{\max} was impaired by 62% when the heart was paced at 180 beats/min but only by 38% when it was beating spontaneously. Bradycardia was probably due to inhibition of the sinus node. It is most marked when vagal tone is reduced or absent (26), which occurs after the administration of either bupivacaine (4,5) or halothane (10,27). The underlying mechanism for the bradycardia probably relates to the ability of both drugs to interfere with the movement of Ca^{2+} across cell membranes of the sinus node and of cardiac and smooth muscle. This has been demonstrated in studies in which calcium channel blockers (i.e., verapamil, diltiazem, and nifedipine) exacerbated decreases in both myocardial contractile performance and hemodynamics caused by bupivacaine. At the same time, slowing of the sinus rate delayed conduction in the atrioventricular node (28-32) and caused a significant increase in toxicity and mortality (33). That interference with the movement of calcium ions causes toxicity is evidenced by experiments in which calcium treatment reversed the increased mortality associated with combined administration of bupivacaine and verapamil (33). Similarly, when verapamil was administered with halogenated anesthetics, its effects on cardiac and smooth muscles (34) as well as on specialized cardiac tissue (27) were exaggerated. Hypercalcemia, which enhances the calcium gradient between the extracellular and intracellular media, counteracts this effect (35). These data suggest that both bupivacaine and halothane oppose the transsarcolemmal entry of Ca^{2+} through calcium

channels, which results in a reduction of intracellular Ca^{2+} concentration (36,37).

In contrast to the above, the actions of bupivacaine and halothane on conduction in ventricular fibers differed from each other. Conduction was greatly depressed by bupivacaine, whereas it remained nearly unchanged with halothane. The reason for this difference probably was that depolarization and conduction in contractile ventricular fibers were based on the inward sodium current of phase 0 of the compound action potential (38,39). This was impeded by bupivacaine, a more potent blocking agent of fast sodium channels than of calcium channels (3,4,40). Halothane predominantly affected the latter channels (20-22), which exclusively govern development of contractile force during phases 1 and 2 of the action potential (38,39).

In the present study, we found that the administration of halothane to group 1 dogs treated with bupivacaine resulted in significant further prolongation of conduction time. However, this did not occur in group 3 dogs when bupivacaine levels were held constant. As halothane is reported to have either no influence (20-22), or at most only a slight influence on intraventricular conduction (41-43), the mechanism of prolongation most likely was indirect, i.e., the increased bupivacaine plasma levels. Increased bupivacaine levels in group 1 dogs were probably secondary to the hypotension that occurred during halothane administration. Hypotension presumably resulted in decreased hepatic perfusion, which would then lead to decreased bupivacaine degradation and reduced clearance (44-47). The lengthening of VERP may also be primarily imputed to this increase in plasma bupivacaine concentration, but pharmacodynamics could have played a role as halothane directly affects VERP (27).

A word of caution is appropriate when interpreting our data. Our experiments were conducted using dogs that were basally anesthetized with chloralose. An anesthetic was necessary to place the catheters and electrodes that were used to study both contractility and conduction and to help maintain the dogs at a steady state while making end-tidal halothane measurements. Chloralose was chosen because it causes only minimal changes in cardiovascular function (48). Nevertheless, it could have enhanced the depressant action of bupivacaine and/or halothane.

In summary, the combined administration of halothane and bupivacaine in a manner that resulted in progressively increasing concentrations of bupivacaine led to significant depression of ventricular contractility and conductivity. By contrast, when circulating bupivacaine concentration was held constant, the administration of halothane resulted in little additive or synergistic depression of ventricular

conductivity. To speculate on the clinical significance of this study, our results suggest a potential clinical danger when halothane and bupivacaine are administered together, particularly if high concentrations of halothane are used such as when general anesthesia is required because the regional block is ineffective. In that situation, systemic bupivacaine absorption could lead to cardiac depression just at the time that the action of halothane would be causing impaired bupivacaine metabolism. It would seem prudent to avoid high concentrations of halothane when bupivacaine is administered.

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Cardiovascular Effects of Volatile Anesthesia in Rabbits: Influence of Chronic Heart Failure and Enalaprilat Treatment

Duncan W. Blake, MB, FFARACS, Diana Way, BSc, Lisbeth Trigg, David Langton, MB, FRACP, and Barry P. McGrath, MD, FRACP

Monash University Department of Medicine, Monash Medical Centre, Prince Henry's Hospital, Melbourne, Australia

Circulatory responses to isoflurane and halothane anesthesia were studied in eight rabbits with biventricular cardiomyopathy induced by doxorubicin (Adriamycin, 14 mg/kg IV over 7 wk) and in eight controls (saline injections). In preliminary operations pulsed-Doppler flow probes were placed on the ascending aorta, left renal artery, and lower abdominal aorta. Each group was studied after 4, 6, and 7 wk of treatment. The development of congestive heart failure (CHF) was associated with decreases in mean arterial pressure and cardiac output (CO) of 14% and 16%, respectively, ($P < 0.05$) and an increase in heart rate. In controls, each anesthetic agent produced dose-related decreases in mean arterial pressure and increases in heart rate, but no significant changes in CO. Renal blood flow was reduced to a similar degree by 1.3 MAC halothane (24% decrease) and 1.3 MAC

isoflurane (21% decrease); hindlimb blood flow was reduced only by halothane. As CHF developed there was an attenuation of the heart rate response to anesthesia. Halothane, but not isoflurane, significantly reduced CO in more advanced stages of CHF. The changes in renal blood flow and hindlimb blood flow with each anesthetic in the CHF group were similar to those observed in controls and did not vary with week of treatment. Administration of the angiotensin-converting enzyme inhibitor enalaprilat (0.2 mg/kg IV) reversed the CO and renal blood flow effects of halothane except after 7 wk of treatment in the CHF group, when the combination of halothane and enalaprilat resulted in severe circulatory depression.

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A preexisting history of congestive heart failure (CHF) significantly increases the risk of morbidity and mortality after noncardiac surgery (1-3). Human CHF may occur with a low, normal, or high cardiac output, although chronic low-output CHF is most common. Low-output chronic CHF is a complex clinical syndrome in which there is increased afterload, activation of neurohumoral vasoconstrictor systems, altered regional blood flow distribution, changes in the cardiorenal axis, and complex functional and structural abnormalities in the failing heart itself. Anesthesia and surgery add a number of potential cardiovascular stress factors for these patients, including direct and indirect myocardial depression and changes in neurohumoral systems and peripheral vascular tone (4,5). With the administration of

volatile anesthetics, reduction in afterload may predominate over direct cardiac depression (6). Although there are major differences between agents (7), systematic study of their effects in CHF has been limited because of the lack of a suitable animal model. Our previous studies have shown that one model of CHF, doxorubicin-induced cardiomyopathy in the rabbit, exhibits many features in common with chronic low-output CHF in humans (8-10).

In the present study the cardiovascular effects of two commonly used volatile anesthetic agents, halothane and isoflurane, were compared at different stages of CHF in doxorubicin-treated rabbits and in control animals. Changes in systemic hemodynamics, in regional blood flows to renal and hindlimb vascular beds, and in plasma renin activity were examined. The rabbits were studied at 4, 6, and 7 wk of treatment during the development of heart failure and at two different levels of anesthesia for each agent. Angiotensin-converting enzyme inhibition is an established treatment of CHF (11,12) and may also have a place in the intraoperative management

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Address correspondence to Dr. Blake, Department of Anaesthesia, Royal Melbourne Hospital, Grattan Street, Parkville, Victoria, Australia 3050.

of CHF (13,14). We therefore also examined the interaction between acute enalaprilat infusion and halothane anesthesia at different stages of CHF.

Methods

Experiments were performed in 16 New Zealand White rabbits weighing 2.3–3.5 kg and aged 14–18 wk. The study was approved by the Prince Henry's Hospital Research Advisory and Ethics Committee and conformed with the guidelines of the National Health and Medical Research Council of Australia.

In eight rabbits, heart failure was induced by the intravenous administration of 1 mg/kg of doxorubicin (Adriamycin, Farmitalia Carlo Erba) twice weekly for 7 wk. A control group of eight rabbits received only saline injections but were handled and housed in a similar manner.

Preliminary surgery was performed after 2 wk of doxorubicin treatment. General anesthesia was induced with 10 mg/kg of intravenous methohexitone and maintained with halothane after endotracheal intubation. An abdominal approach was used to implant pulsed-Doppler flow probes (1-mm² crystals) on the left renal artery and on the abdominal aorta just above its bifurcation (15). A left thoracotomy was also performed and a Doppler probe was applied to the ascending aorta. Wires from each crystal were buried subcutaneously. After surgery, doxorubicin treatment was not restarted for at least 1 wk and was interrupted if the rabbit was losing weight. The initial experiments were performed after completion of 4 wk of doxorubicin treatment and were therefore separated from the surgery by at least 3 wk.

On each experimental day, catheters were placed in an ear artery and vein and the Doppler wires were exteriorized using 0.5% lignocaine local anesthesia. The rabbits were then placed in a sealed Perspex box supplied with 4 L/min of a mixture of air and oxygen. Resting observations were made over the 30 min before administration of halothane or isoflurane.

Mean arterial pressure (MAP) was measured using a Hewlett-Packard transducer and was used to trigger a pulse-interval meter (Baker Medical Research Institute, Melbourne, Australia). All signals were continuously recorded on computer (Macintosh SE, Apple Computer Inc., Cupertino, Calif.) using an A/D converter (MacLab, Analog-Digital Instruments, Dunedin, New Zealand). The three Doppler crystals were connected to a pulsed-Doppler flowmeter (model 545C-3; Bioengineering, University of Iowa, Iowa City, Iowa). Flows were measured as kilohertz Doppler shift and calibrated with a frequency generator. Doppler signals from the renal artery (renal blood flow, RBF) and lower aorta (hindlimb blood flow,

HBf) were adjusted using the range control to give maximum output and the clearest signal. These Doppler crystals were mounted in Dacron cuffs and required readjustment of the range at each experiment, so that it was not possible to compare resting levels of RBF and HBf over the 3-wk experimental period. The ascending aorta Dopplers were mounted in polystyrene shells and were used to measure cardiac output (CO) after adjustment to detect the axial flow signal. This system was calibrated against thermodilution CO using an aortic thermistor in a separate series of four rabbits. A linear correlation ($r^2 = 0.92$) was obtained over the range 0.5–1.5 L/min.

The volatile anesthetic agents were delivered in oxygen from Fluotec Mark 2 vaporizers at a flow rate of 4 L/min. The anesthetic concentration in the exit gas from the rabbit box was measured continuously with a crystal detector (Servo Gas Monitor 120, Siemens-Elema AB, Sweden).

Experiments were performed in three groups: after 4, 6, and 7 wk of doxorubicin treatment, or after similar periods in the control group. The volatile anesthetics were each administered for 30 min at 0.7 MAC (minimum alveolar concentration) for the rabbit and then at 1.3 MAC for 30 min. This corresponds to 1 and 2 vol% halothane and 1.5 and 3 vol% isoflurane (16). In each group of experiments, there was a recovery period of at least 4 h between the administration of halothane and isoflurane, and the order of administration was randomized. The two concentrations of each anesthetic were administered for consecutive 30-min periods during which an approximate steady state was reached as indicated by the cardiovascular variables. Mean arterial pressure, CO, heart rate, RBF, and HBf were averaged for the final 10 min at each anesthetic concentration. Arterial blood samples (0.5 mL) were also taken for blood gas analysis and renin assays at this time. The samples for renin assay were collected on ice, immediately centrifuged, and the plasma was stored at –20°C until assayed by radioimmunoassay (17).

The effect of enalaprilat on the response to halothane was studied on a separate day. After the initial rest period, enalaprilat was administered as a 0.2-mg/kg intravenous bolus followed by an infusion of 0.003 mg·kg^{–1}·min^{–1}. This regimen reduces converting enzyme activity in the rabbit to less than 3% of control (18). Measurements were averaged for 10-min periods: 20 min after starting the enalaprilat, after 30 min of 0.7 MAC halothane, and after 30 min of 1.3 MAC halothane.

Levels of the hemodynamic variables were compared by analysis of variance. The factors used were rabbits, anesthetics, enalaprilat treatment, week of study, and doxorubicin treatment. Specific contrasts were made by partitioning of the analysis of variance.

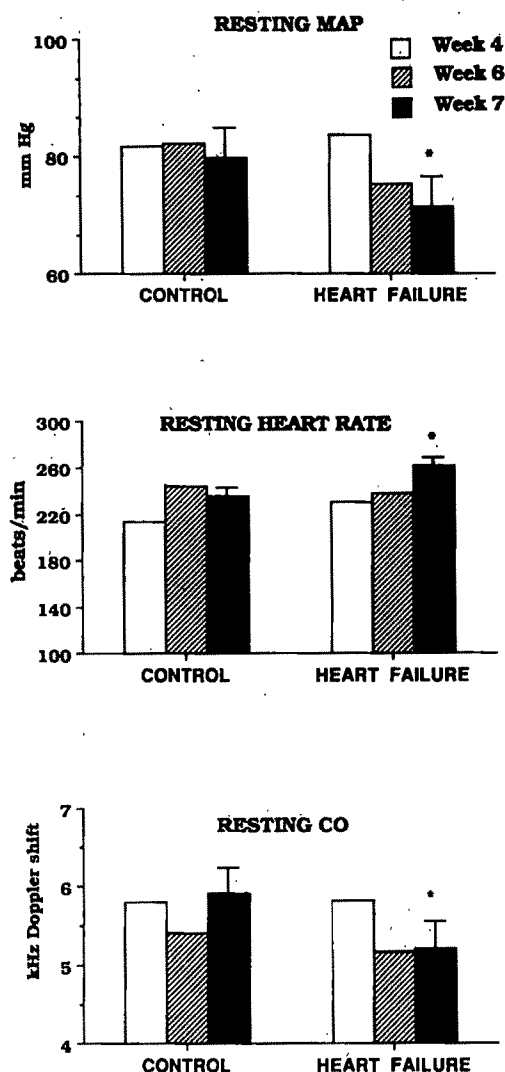


Figure 1. Mean arterial pressure (MAP), heart rate, and cardiac output (CO) in conscious resting rabbits after 4, 6, and 7 wk of treatment. Left: control group ($n = 8$), saline injections only. Right: heart failure group ($n = 8$), doxorubicin (1 mg/kg IV twice weekly). Error bars indicate SEM for each experimental group derived from analysis of variance. SEM = (error mean square/ n)^{1/2}. * $P < 0.05$ for orthogonal comparisons of means.

The Bonferroni correction was made to multiple, nonorthogonal contrasts. In the figures, the hemodynamic variables are shown as between-rabbit means with error bars indicating 1 standard error of the mean (SEM).

Results

Conscious Animals

Resting hemodynamic measurements in the two groups are shown in Figure 1. The control group showed no significant change in resting MAP, CO, heart rate, or regional blood flows with time. In the

doxorubicin-treated group, there was a reduction after 6 wk in MAP (14%, $P < 0.05$) and CO (16%, $P < 0.05$) and a 13% increase in heart rate ($P < 0.01$) at 7 wk.

Anesthesia

The rabbits tolerated each anesthetic without apparent distress. At the lower concentration (0.7 MAC) of each agent, they continued to move spontaneously in the experiment box and would react to external stimuli. The higher concentration (1.3 MAC) induced general anesthesia and, although ventilation was not controlled, respiratory rate was unchanged. The degree of respiratory depression did not differ between the anesthetic agents or with the development of CHF. With 1.3 MAC anesthesia, the mean partial arterial pressure of carbon dioxide for both groups was only slightly raised from 29.6 ± 1.4 to 35.1 ± 2 mm Hg and, with an inspired oxygen concentration of 70%, the mean partial arterial pressure of oxygen was 322 ± 19 mm Hg.

There was no significant change in the circulatory responses of the control group to either anesthetic over the 3-wk experimental period (Table 1), so in Figures 2-5 the average result from the three experiments in normal rabbits is shown in the left panel (control). At 1.3 MAC, halothane and isoflurane reduced MAP in normal rabbits by 17% and 19%, respectively (Figure 2, $P < 0.01$). This was associated with similar increases in heart rate with each anesthetic (halothane from 230 to 293 beats/min, $P < 0.005$; isoflurane from 240 to 294 beats/min, $P < 0.005$). Cardiac output was not changed significantly with either anesthetic (Figure 3), but at 1.3 MAC halothane reduced RBF by 24% ($P < 0.05$) and isoflurane reduced RBF by 21% ($P < 0.05$). At 1.3 MAC halothane reduced HBF by 21% ($P < 0.05$), but isoflurane did not significantly alter HBF.

In the CHF group, resting MAP was lower after 6 and 7 wk of doxorubicin treatment. At the lower concentration (0.7 MAC), halothane did not significantly alter MAP at any stage of doxorubicin treatment, but 0.7 MAC isoflurane reduced MAP by 7% (5 ± 2 mm Hg, $P < 0.05$) after 6 and 7 wk of drug treatment. At this stage of CHF, 1.3 MAC halothane and isoflurane had similar effects on MAP. The average decrease in MAP of 22% (16 ± 4 mm Hg) was similar to that in controls, but the hypotension during anesthesia was more pronounced because of the lower resting MAP ($P < 0.05$). In the CHF group, the heart rate during anesthesia did not change at weeks 4, 6, and 7 of doxorubicin treatment. However, resting heart rate increased with the development of cardiac failure and the responses to each anesthetic

Table 1. Comparison Between the Responses to Anesthesia in Eight Control Rabbits at 4, 6, and 7 Weeks of the Study

			Change due to anesthesia				
Week	MAC	Agent	MAP (mm Hg)	HR (beats/min)	CO (kHz Ds)	RBF (kHz Ds)	HBF (kHz Ds)
4	0.7	H	2	35	0.4	-0.2	0.4
		I	-3	50	0.4	-0.4	-0.5
	1.3	H	-16	63	-0.1	-1.3	-1
		I	-10	68	0.1	-1.4	-0.4
6	0.7	H	4	39	0.1	-0.8	-1.1
		I	-2	38	-0.1	-0.6	-0.4
	1.3	H	-15	40	-0.4	-1.7	-2.4
		I	-16	38	-0.3	-1.1	0.1
7	0.7	H	-3	27	0.4	0.4	0.4
		I	-11	51	0.2	-0.8	-0.6
	1.3	H	-10	52	0.7	-1.4	-0.1
		I	-18	50	0.8	-1.5	-1.1
F (2,12 df) between weeks			1.01	2.05	2.62	2.75	1.09
			NS	NS	NS	NS	NS

kHz Ds, kilohertz Doppler shift; H, halothane; I, isoflurane; MAP, mean arterial pressure; HR, heart rate; CO, cardiac output; RBF, renal blood flow; HBF, hindlimb blood flow; F, within-animal comparison of response at 4, 6, and 7 wk by analysis of variance; NS, not significant ($P > 0.05$).

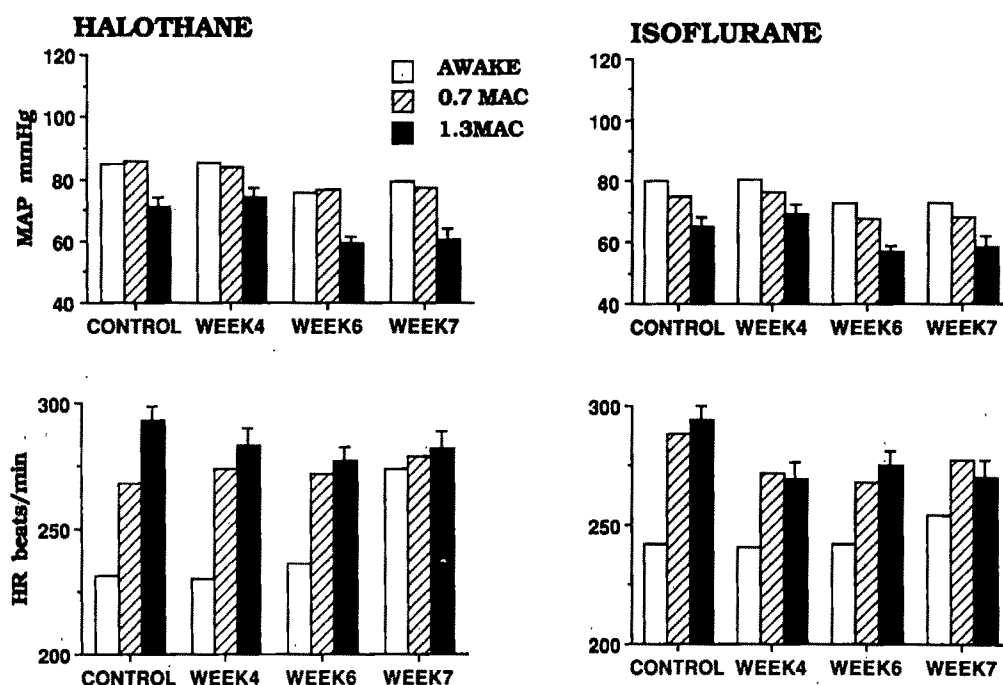


Figure 2. Mean arterial pressure (MAP) and heart rate (HR) in two groups of rabbits and at two anesthetic concentrations (0.7 and 1.3 MAC) for halothane and isoflurane anesthesia. The averaged responses of the control group ($n = 8$) for the three experiments are shown at the left of each panel. The results for the CHF group are shown as weeks 4, 6, and 7 of treatment. Error bars indicate standard error of mean from analysis of variance.

were significantly attenuated after 6 wk of treatment ($P < 0.05$ for treatments \times times interaction, Figure 2).

Anesthetic-induced changes in CO, RBF, and HBF with weeks of doxorubicin treatment are shown in Figure 3 together with the mean changes in the control group. In the CHF group, CO was not signif-

icantly changed by isoflurane anesthesia at 0.7 or 1.3 MAC. However, there was a progressively greater decrease in CO due to 1.3 MAC halothane with the development of CHF, reaching 20% at the 7-wk study ($P < 0.05$). In the CHF group, 0.7 MAC halothane reduced RBF by an average of 8% and 0.7 MAC

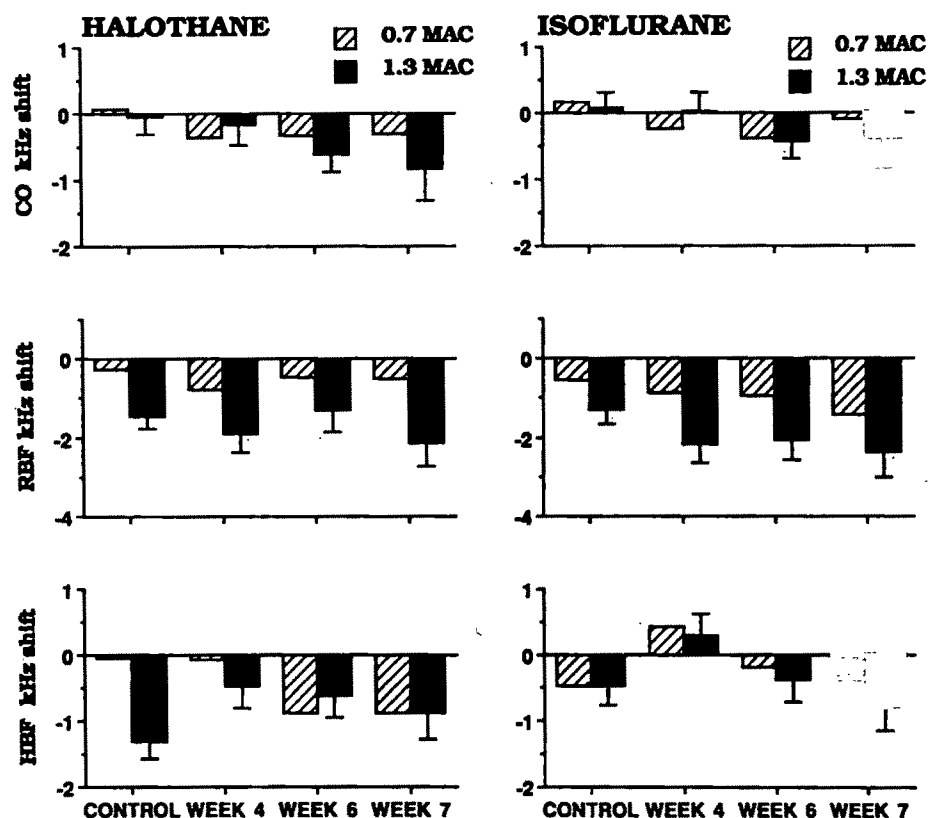


Figure 3. Change from mean awake values at two concentrations of halothane and isoflurane for cardiac output (CO), renal blood flow (RBF), and hindlimb blood flow (HBF) in two groups of rabbits: controls ($n = 8$, average responses) and CHF ($n = 8$, weeks 4, 6, and 7 of treatment). Blood flows measured as kHz Doppler shift from chronically implanted pulsed-Doppler flowmeters. Error bars indicate standard error of mean change.

isoflurane reduced RBF by 15% ($P < 0.05$). At 1.3 MAC, RBF decreased by 25% with halothane and 30% with isoflurane ($P < 0.01$). These RBF responses did not differ significantly between anesthetics, between the control and CHF groups, or between weeks within the groups. No significant changes in HBF were found with isoflurane anesthesia. After 7 wk of treatment with doxorubicin, there was a decrease in HBF of 18% during halothane anesthesia ($P < 0.05$), similar to the 21% decrease observed in the control group.

Plasma renin concentrations increased with anesthesia, but there was no significant difference between the responses to halothane and isoflurane. The average renin increase of 16.1 ng/mL in the CHF group at 7 wk was significantly greater ($P < 0.005$) than the increase of 9.6 ng/mL in the controls.

Enalaprilat Infusion

In conscious controls, enalaprilat caused a small decrease in MAP and increase in heart rate (Figure 4). During enalaprilat infusion, there was a progressive reduction in MAP with 0.7 and 1.3 MAC halothane ($P < 0.05$), and MAP was significantly lower than with halothane alone ($P < 0.01$). The increase in heart rate with enalaprilat and halothane ($P < 0.005$) was

similar to that with halothane alone. During enalaprilat infusion, resting CO and RBF were increased in control rabbits by 17% ($P < 0.05$) and by 20% ($P < 0.025$), respectively (Figure 5). The decrease in RBF seen during halothane anesthesia was abolished by the enalaprilat infusion.

In the CHF group, enalaprilat again caused a further reduction in MAP during halothane anesthesia (Figure 4). After 7 wk of doxorubicin treatment, MAP decreased by 34% from 70 mm Hg (resting) to 46 mm Hg (standard error of difference, 5 mm Hg) with enalaprilat plus 1.3 MAC halothane. Cardiac output during halothane plus enalaprilat was maintained in the CHF group except after 7 wk of doxorubicin treatment when CO decreased with 1.3 MAC halothane (Figure 5). In CHF rabbits enalaprilat also prevented the decrease in RBF produced by halothane anesthesia at both 0.7 and 1.3 MAC, except during the higher anesthetic dose after 7 wk of doxorubicin treatment. Enalaprilat infusion had little effect on the HBF changes during halothane anesthesia (Figure 5).

Discussion

Activation of neurohumoral systems in CHF results in peripheral circulatory changes, redistribution of

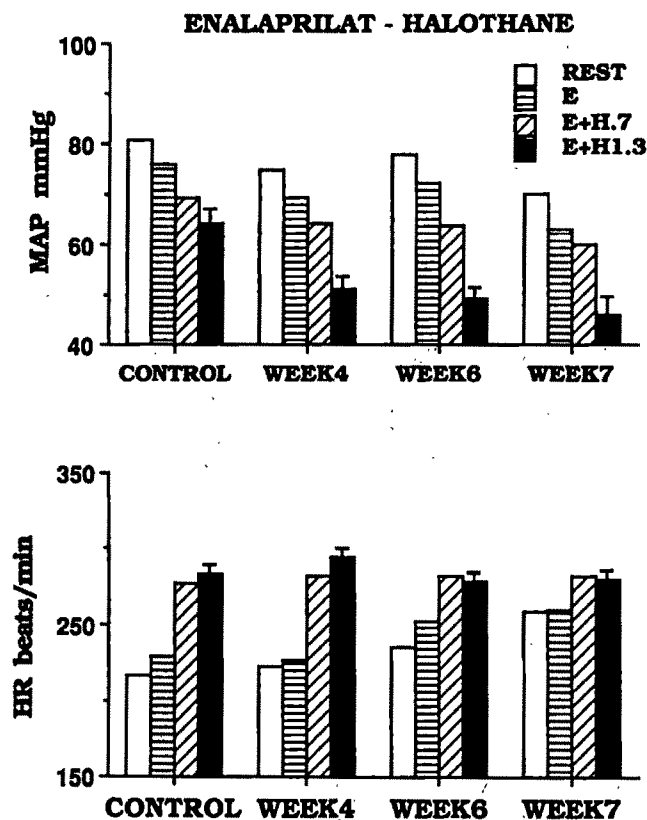


Figure 4. Mean arterial pressure (MAP) and heart rate (HR) in the conscious rabbits (*Rest*), during enalaprilat infusion (*E*), enalaprilat with 0.7 MAC halothane (*E+H.7*), and enalaprilat with 1.3 MAC halothane (*E+H1.3*). Averaged responses of the control group are shown on the left, and the responses in the group with heart failure after 4, 6, and 7 wk of treatment are shown on the right. Error bars indicate standard error of mean change from analysis of variance.

CO, increased cardiac load, and further deterioration in function. Ventricular irritability is also increased and there is a high incidence of sudden death (19). It is not surprising, therefore, that the Goldman index alone will not identify many patients who are at risk (1,20). Patients with mild-to-moderate CHF frequently require anesthesia, particularly for associated coronary or peripheral vascular disease. Their increased morbidity may be related to alterations in the pattern of cardiovascular responses to individual anesthetic drugs, but this is difficult to determine in humans.

The pathological, hemodynamic, and hormonal changes associated with doxorubicin-induced CHF in the rabbit have been described in previous studies (8-10) and reflect the changes associated with CHF in humans. Over a 7-wk period, the rabbits develop a severe cardiomyopathy with interstitial fibrosis, biventricular dilatation, and hypertrophy. Exercise capacity is reduced progressively as the cumulative dose of doxorubicin increases (21). There is a high mortality after 7 wk of treatment, and ascites and

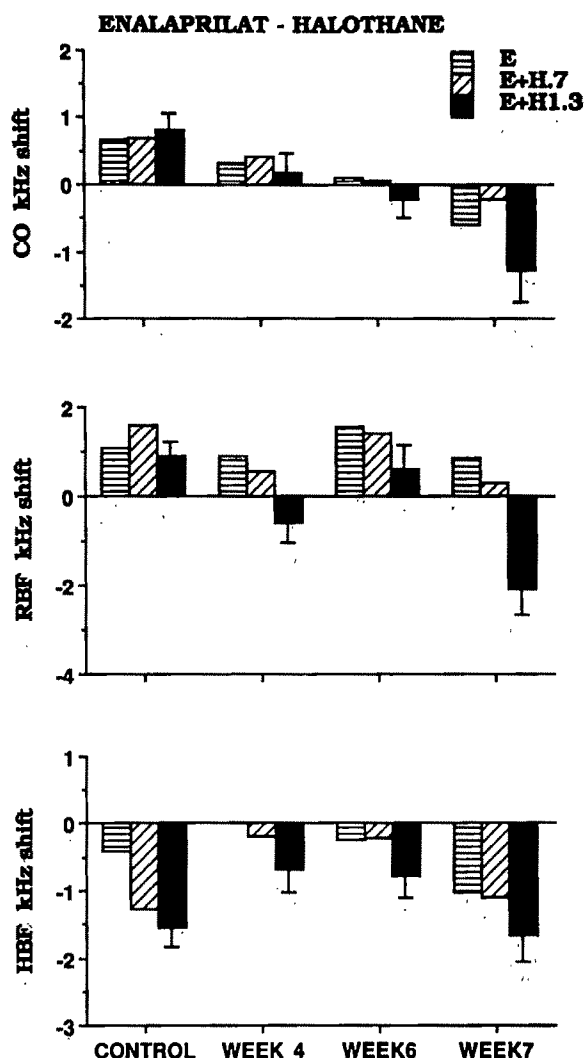


Figure 5. Changes from resting in cardiac output (CO), renal blood flow (RBF), and hindlimb blood flow (HBF) during enalaprilat infusion (*E*), enalaprilat with 0.7 MAC halothane (*E+H.7*), and enalaprilat with 1.3 MAC halothane (*E+H1.3*). The left panel shows the average responses in the control group, and responses in the group with heart failure after 4, 6, and 7 wk of treatment are shown on the right. Error bars indicate standard error of mean change from analysis of variance.

pleural effusions are commonly found at postmortem. There is a progressive increase in plasma noradrenaline and in plasma renin activity between 4 and 8 wk despite an increased blood volume. Renal blood flow measurements using either radiolabeled microspheres or [125 I]orthoiodohippurate show an early reduction, before any reduction in CO, although renal histology and mesenteric blood flow are unchanged. Renal sympathetic nerve activity (RSNA) is increased after only 4 wk of treatment and baroreceptor-induced changes in RSNA are increased early but blunted late in this model of CHF (22). In the present study, responses to anesthesia were tested between 4 and 7 wk of doxorubicin treatment to

correspond with early and established heart failure. In conscious rabbits, the MAP, CO, and heart rate changes associated with the development of CHF were similar to those previously described. With the pulsed-Doppler technique it was not possible to measure absolute levels of RBF and HBF or to compare flows at different stages of CHF. However, the technique did allow changes in regional blood flows to be determined during the acute experiments.

The cardiovascular responses to anesthesia of the control rabbits in the present study were similar to responses in humans. There were dose-related decreases in MAP and RBF with both isoflurane and halothane. Only halothane reduced hindlimb (muscle) blood flow. With isoflurane HBF was maintained, consistent with its vasodilator effect in muscle. However, neither anesthetic significantly reduced CO in normal rabbits, which is in contrast to the effect of halothane on CO in humans. Cardiac output was maintained during halothane anesthesia in the rabbit by a marked increase in heart rate not found in humans. The rabbit has a small heart size relative to body weight, and changes in CO are primarily determined by changes in heart rate rather than by stroke volume. Both isoflurane and halothane reduce RBF in humans (23,24), but there are conflicting reports on the RBF effects of isoflurane from animal studies (25,26). The effects seen in this study in rabbits are similar to those observed in humans.

The reduction in RBF owing to anesthesia was similar with both volatile anesthetics. Neurohumoral mechanisms are likely to be responsible for this, including an increase in RSNA. Volatile anesthetics are potent depressors of arterial baroreceptor responses (7). Therefore, an increase in renal sympathetic tone during anesthesia might be due to removal of an inhibitory effect on the RSNA from baroreceptor-dependent pathways.

As CHF developed with doxorubicin treatment, there was an attenuation of the heart rate response to halothane and isoflurane anesthesia. This is consistent with the progressive impairment of arterial baroreceptor function in this model (22). Both anesthetic agents were associated with absolute decreases in MAP and RBF in the animals with heart failure that were similar to those in controls. However, the lower resting values increase the significance of the blood pressure changes. Although absolute resting RBF was not determined in this study, it is known to be reduced by 30% after 6 wk of doxorubicin treatment and decreases further thereafter (10). Therefore, the dose-related decreases observed in RBF with each anesthetic in the CHF group are also very significant.

Halothane, but not isoflurane, reduced CO in the more advanced stages of CHF in this study. Studies of isolated cardiac muscle suggest that direct cardiac

depression owing to halothane is not potentiated in CHF, but the net reduction in contractility may be more significant (27). Combined with the blunted heart rate response to anesthesia, this could explain the decrease in CO seen in the CHF group, but not in controls. Isoflurane has been reported to have a smaller negative inotropic effect than halothane in animal studies, and this is supported by clinical observations (5,28,29). Hindlimb blood flow was also maintained during isoflurane anesthesia, but not with halothane. The changes in HBF, reflecting predominantly muscle blood flow, were similar in CHF and control rabbits. In this model of CHF, we have previously shown that exercise induces an exaggerated sympathetic vasoconstriction in both the renal and hindlimb vascular beds (30,31). In the present study, no such exaggerated response was found with anesthesia.

Plasma renin levels increased with each anesthetic in both the control and CHF rabbits. In the rabbit, renin release occurs even with mild stress such as the insertion of an intravenous catheter (32). This may have accounted for part of the renin release, but not for the difference between the control and CHF groups. Both increased sympathetic activity and reduced RBF would be likely factors contributing to the exaggerated renin response in the CHF group.

Enalaprilat has been shown to improve survival in severe CHF in humans and may also improve exercise capacity (11,33), although the mechanisms are unknown. In patients without cardiac failure, preoperative enalaprilat reduces MAP during anesthesia but does not influence the autonomic responses to postural change or endotracheal intubation (34). The effect of intraoperative intravenous enalaprilat treatment of a patient with CHF has recently been reported (14). After the acute development of left-ventricular failure, enalaprilat greatly increased CO and reduced heart rate with only a small reduction in MAP. In the present study, acute administration of intravenous enalaprilat in rabbits with CHF produced an increase in CO and RBF with only minor changes in MAP and heart rate. This favorable response was obtained at each stage of CHF studied. Enalaprilat infusion, commenced before halothane administration, prevented the decrease in RBF in both control and CHF rabbits. This occurred despite a greater decrease in MAP than with halothane alone. Only at the 7-wk stage of CHF was RBF reduced by the higher concentration of halothane and enalaprilat.

Despite the activation of several vasoconstrictor systems and a reduction in cardiac reserve in this model of CHF, differences in the cardiovascular effects of halothane and isoflurane were not particularly exaggerated, although isoflurane caused less hemodynamic disturbance than halothane. The re-

sults suggest that higher concentrations of halothane can reduce CO to critical levels and that either anesthetic may cause a severe reduction in RBF, even when CO is maintained. Although the use of angiotensin-converting enzyme inhibitors in CHF is well established, further clinical studies are needed to determine their role in the perioperative period. Enalaprilat infusions during anesthesia in patients with CHF may reduce morbidity caused by regional ischemia. The present study found a relatively severe circulatory depression with the combination of halothane and enalaprilat in the presence of late CHF. This was not unexpected as the use of a potent myocardial depressant is likely to block the reflex increase in CO that normally follows the afterload reduction caused by enalaprilat. It may be necessary to avoid higher concentrations of volatile anesthetics during enalaprilat treatment in patients with heart failure.

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Halothane Increases Epinephrine Threshold for the Development of Slow Responses in Isolated Canine Trabeculae

Shuzo Oshita, MD, Hideo Oka, MD, Izumi Hiraoka, MD, and Hiroshi Takeshita, MD

Department of Anesthesiology, Yamaguchi University Hospital, Ube, Yamaguchi, Japan

We studied halothane/epinephrine interaction in isolated canine trabeculae using the doses of epinephrine necessary to produce slow responses (epinephrine threshold for the development of slow responses, ETSR) as an indicator. The preparations were depolarized in Tyrode's solution containing 26 mmol/L of KCl, then epinephrine concentrations in the solution were increased in a stepwise manner. Halothane (1%) had no significant effect, whereas 2% and 4% halothane significantly increased the ETSR. α_1 -Blockade with either 4, 8, or 16 ng/mL of prazosin or 20, 40, or 80 ng/mL of droperidol did not alter the ETSR, whereas β_1 -adrenergic blockade with 8, 17, or 34 ng/mL of metoprolol significantly increased the ETSR. The same trend was observed when either

8 ng/mL of prazosin or 17 ng/mL of metoprolol was given in combination with 2% halothane. Verapamil (5, 10, or 20 ng/mL) increased the ETSR in a dose-dependent manner. These results indicate that halothane decreases rather than increases the sensitivity of slow calcium channels to epinephrine and that any increase above the baseline ETSR after halothane administration cannot be ascribed to halothane/adrenoceptor interaction but rather to calcium entry-blocking effects of halothane. As slow responses are induced by the activation of slow calcium channels, our findings are consistent with known data that halothane can interfere with slow calcium channel conductance.

(Anesth Analg 1991;73:449-54)

Halothane reduces the dose of epinephrine required to produce ventricular arrhythmias both in experimental animals (1) and in patients (2). This phenomenon has been called halothane-induced "sensitization" of the myocardium. Maze and Smith (3) recently postulated that halothane directly sensitizes the myocardium to epinephrine, whereas Zink et al. (4) and Atlee and Bosnjak (5) suggested that halothane's influence on the myocardium is not responsible for the more sensitive response to the arrhythmogenic properties of epinephrine. Katz and Epstein (6) stated that myocardial β -adrenoceptors were more responsible, whereas Maze and Smith (3), Spiss et al. (7), and Maze et al. (8) suggested that myocardial α_1 - rather than β_1 -adrenoceptors are predominant in the halothane/epinephrine interaction. These uncertainties are largely due to the fact that most previous studies were performed in the in vivo experimental model in which data are affected by many factors—

hemodynamic, neural, and metabolic—as well as by the direct effects of drugs on the myocardium. Accordingly, in vitro experiments may be necessary to explore the direct effects of halothane on the myocardial sensitivity to epinephrine.

In isolated, partially depolarized, guinea pig myocardium, Ehara et al. (9) studied the effects of temperature on the myocardial sensitivity to catecholamines using the sensitivity of slow calcium channels to catecholamines as an indicator. In their experimental model, catecholamine-induced increases in slow channel conductance produced a depolarization of the resting membrane in quiescent ventricular muscle. The depolarization was enhanced and often led to an automatic activity as temperature decreased. These results suggest that the sensitivity of slow calcium channels to catecholamines reflects, at least in part, myocardial sensitivity to catecholamines and that the sensitivity of myocardium to catecholamines is increased at lower temperatures. To explore the halothane/epinephrine interaction in an in vitro experimental model, we also used the sensitivity of slow calcium channels to epinephrine, i.e., the doses of epinephrine necessary to produce slow responses (epinephrine threshold for the development of slow

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Address correspondence to Dr. Oshita, Department of Anesthesiology, Yamaguchi University Hospital, Ube, Yamaguchi 755, Japan.

responses, ETSR) as an indicator and studied the effects of halothane, selective α_1 - (prazosin, droperidol) and β_1 - (metoprolol) adrenergic receptor antagonists, and calcium entry blocker (verapamil), alone or in combination with halothane, on the ETSR in isolated, partially depolarized canine trabeculae.

Methods

Our protocol was approved by the animal investigation committee of the hospital. Thirty-five unpremedicated mongrel dogs of either sex weighing 13–21 kg were anesthetized with 3% enflurane in oxygen. The trachea was intubated and the lungs were ventilated through a volume-limited Harvard pump. The beating heart then was removed by sternotomy and was immediately placed in oxygenated Tyrode's solution at room temperature. The trabeculae (greater than 10 mm in length and 1–2 mm in diameter) were dissected from the right ventricle and were pinned on a small silicon rubber platform. The preparations were stimulated with constant-current pulses introduced at the cut end through small bipolar Ag/AgCl electrodes. The stimulation rate was 0.5 Hz, and the stimuli were either of 1-ms duration and barely above threshold (mostly 1 mA) in standard Tyrode's solution (concentrations in mmol/L: NaCl, 125; KCl, 5.4; CaCl_2 , 1.8; MgCl_2 , 1.05; NaHCO_3 , 24; NaH_2PO_4 , 0.42; and glucose, 5.5), or of 10-ms duration and 5 mA in strength in K^+ -rich Tyrode's solution containing 26 mmol/L of KCl. Individual preparations were equilibrated for at least 60 min in standard Tyrode's solution before the start of experiments, then they were depolarized with K^+ -rich Tyrode's solution to determine ETSR. Standard and K^+ -rich Tyrode's solution were aerated with 95% O_2 /5% CO_2 , and the pH of both solutions were maintained at 7.3–7.4.

Vigorous contractions due to epinephrine frequently dislodged the intracellular electrode. Hence, the cardiac electrograms were recorded from the surface of the preparations. In our experimental model, high extracellular resistance was essential to obtain a reliable extracellular voltage drop along the preparations. For this purpose, the preparations were surrounded with a uniform and very thin layer of Tyrode's solution. The perfusion apparatus has been previously described and illustrated (10). Briefly, the preparations, pinned on a small silicon rubber platform, were covered by a single layer of cotton mesh. One end of the preparation was placed at the lumen of a 1-mm tube through which oxygenated 37°C Tyrode's solution flowed at a rate of 3 mL/min maintained constant by a roller perfusion pump. A similar tube was placed at the other end and connected to a suction apparatus that was carefully adjusted to provide a thin layer of fluid around the preparations.

Two glass microelectrodes filled with 3 mol/L of KCl (resistance 10–20 M Ω) were used to record cardiac electrograms. One recording electrode was placed 1–1.5 mm from the stimulation electrodes, and the other reference electrode was placed just beyond the preparation in the fluid stream coming from the perfusion tubing. Extracellular voltage drop was recorded by differential-input high-impedance amplifier (Nihon Kohden AVM-10) coupled with a cathode follower (Nihon Kohden MEZ-7101) and displayed on a Nihon Kohden VC-10 oscilloscope.

Fast sodium channels were inactivated by partially depolarizing the preparations in K^+ -rich Tyrode's solution, and slow calcium channels were activated by adding epinephrine to the solution. Propagating slow responses were generated when the epinephrine concentrations in the solution reached ETSR. In the present study, ETSR was defined as the dose of epinephrine required to produce nine or more continuous or intermittent slow responses within the last 3 min of a 15-min infusion, which was sufficient time to produce stable effects. If the ETSR was not achieved during 15 min of constant infusion at one concentration of epinephrine, another solution containing a standardized logarithmically spaced higher dose of epinephrine (i.e., 1.58, 2.00, 2.51, 3.16, etc., $\times 10^{-7}$ mol/L) was infused, and the procedure was repeated until the ETSR was established.

The ETSR was determined before (baseline) and 30 min after administration of each concentration of halothane (1%, 2%, 4%, $n = 7$), prazosin (4, 8, 16 ng/mL, $n = 7$), and metoprolol (8, 17, 34 ng/mL, $n = 7$). The ETSR was also determined at 2% halothane, alone or in combination with either 8 ng/mL of prazosin or 17 ng/mL of metoprolol ($n = 8$). In a separate set of experiments, the effects of droperidol (20, 40, 80 ng/mL, $n = 3$) and verapamil (5, 10, 20 ng/mL, $n = 3$) on the ETSR were evaluated. Halothane was equilibrated with Tyrode's solution in reservoir by passing the 95% O_2 /5% CO_2 through the calibrated vaporizer for at least 30 min before application to the preparation. The concentrations of 1%, 2%, and 4% halothane in solution, verified by gas chromatography (Shimadzu GC-4), were 9.6 ± 0.2 , 22.5 ± 0.7 , and 41.3 ± 0.5 mg/dL (mean \pm SEM, $n = 8$ –10), respectively. Other drugs were dissolved in Tyrode's solution at each concentration. The initial concentration and the order of subsequent concentrations of drugs were randomized to avoid a possible systematic time-dependent effect.

One-way analyses of variance with critical-difference testing were used to determine statistical significance between the baseline values and the values obtained at each concentration for each drug. A P value of <0.05 was considered statistically significant.

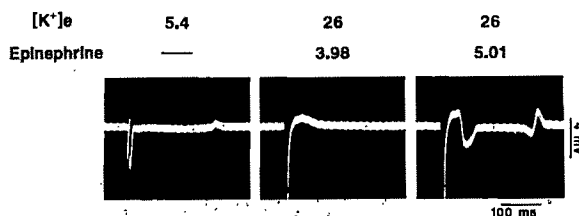


Figure 1. Typical cardiac electrograms recorded from a canine trabeculae placed on a small silicon rubber platform and surrounded with a thin layer of Tyrode's solution. $[K^+]_e$ and epinephrine in this figure represent extracellular potassium (mmol/L) and epinephrine concentrations ($\times 10^{-7}$ mol/L), respectively. Note that in standard Tyrode's solution (left panel), the biphasic deflection of the initial complexes of the cardiac electrograms was very rapid, suggesting the genesis of fast responses, whereas in K^+ -rich Tyrode's solution containing 3.98×10^{-7} mol/L epinephrine (middle panel), the initial deflection was very slow, suggesting the genesis of slow responses. Only a stimulation artifact was obtained in K^+ -rich Tyrode's solution containing 5.01×10^{-7} mol/L epinephrine (right panel).

Results

Figure 1 illustrates representative electrograms recorded from the surface of the same preparation. As can be seen in the left panel of this figure, cardiac electrograms characterized by the biphasic and rapid deflection of the initial complexes and by the following isoelectric ST segments and T waves (11) were recorded in standard Tyrode's solution. In K^+ -rich Tyrode's solution, only a stimulation artifact was recorded at 3.98×10^{-7} mol/L of epinephrine (middle panel), whereas cardiac electrograms with very slow deflection of the initial complexes were obtained at 5.01×10^{-7} mol/L of epinephrine (right panel). Because the initial positive-negative deflection corresponds in time to the upstroke of the transmembrane action potential (11), cardiac electrograms with rapid deflection indicate the genesis of fast responses (left panel), whereas those with slow deflection indicate the genesis of slow responses (right panel). As more than nine slow responses were obtained within the last 3 min in K^+ -rich Tyrode's solution containing 5.01×10^{-7} mol/L of epinephrine, the ETSR at this condition was determined as 5.01×10^{-7} mol/L.

The mean ETSR values obtained before (baseline) and at each concentration for each drug are shown in Figures 2-6. As shown in Figure 2, 1% halothane had no significant effect, whereas 2% and 4% halothane significantly increased the ETSR twofold and fivefold, respectively. α_1 -Blockade with either 4, 8, or 16 ng/mL of prazosin (Figure 3) or 20, 40, or 80 ng/mL of droperidol (Figure 6) did not alter the ETSR, whereas β_1 -blockade with 8, 17, and 34 ng/mL of metoprolol significantly increased the ETSR twofold, fourfold, and sixfold, respectively (Figure 4). The effects of 8 ng/mL of prazosin and 17 ng/mL of metoprolol when given in combination with 2%

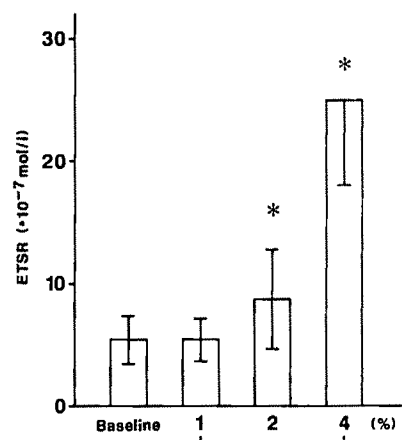


Figure 2. Epinephrine threshold for the development of slow responses (ETSR) at different concentrations of halothane. Bars represent mean \pm SEM. *Significantly different from the baseline value.

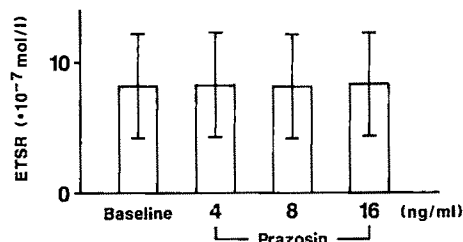


Figure 3. Epinephrine threshold for the development of slow responses (ETSR) at different concentrations of prazosin. Bars represent mean \pm SEM.

halothane were almost the same as those obtained for either drug given alone. Compared with the ETSR obtained at 2% halothane, 8 ng/mL of prazosin did not alter the ETSR, whereas 17 ng/mL of metoprolol significantly increased the ETSR fivefold (Figure 5). Verapamil (5, 10, and 20 ng/mL) increased the ETSR in a dose-dependent manner (Figure 6).

Discussion

Our study differs from previous investigations because the direct effects of halothane on myocardial sensitivity to epinephrine and the adrenoceptor mechanisms that mediate halothane/epinephrine interaction in isolated heart preparations were studied. As in the study of Ehara et al. (9), we also used the sensitivity of slow calcium channels to epinephrine, i.e., the ETSR, as an indicator for myocardial sensitivity to epinephrine. As epinephrine exerts its effects on the heart by increasing the slow channel conductance (12), which is triggered by epinephrine/adrenoceptor interaction, the responsiveness of slow calcium channels to epinephrine in isolated heart

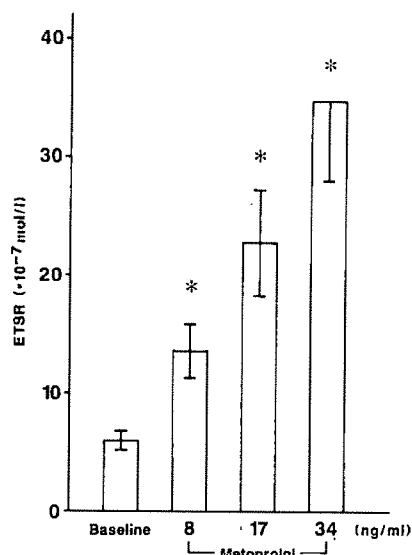


Figure 4. Epinephrine threshold for the development of slow responses (ETSR) at different concentrations of metoprolol. Bars represent mean \pm SEM. *Significantly different from the baseline value.

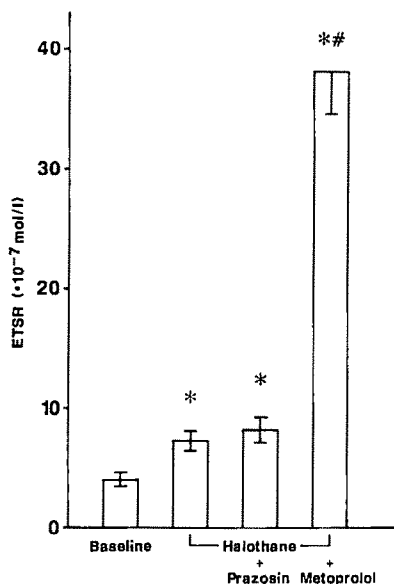


Figure 5. Epinephrine threshold for the development of slow responses (ETSR) at 2% halothane alone or in combination with either 8 ng/mL of prazosin or 17 ng/mL of metoprolol. Bars represent mean \pm SEM. *Significantly different from the baseline value. #Significantly different from the value obtained at 2% halothane.

preparations should reflect, at least in part, cardiac responses to epinephrine. Activation of the slow calcium channel initiates slow responses. The cellular electrophysiologic mechanisms for the occurrence of arrhythmias involve altered normal automaticity, abnormal automaticity, triggered activity, and reentry (5), and among them, slow responses are thought to

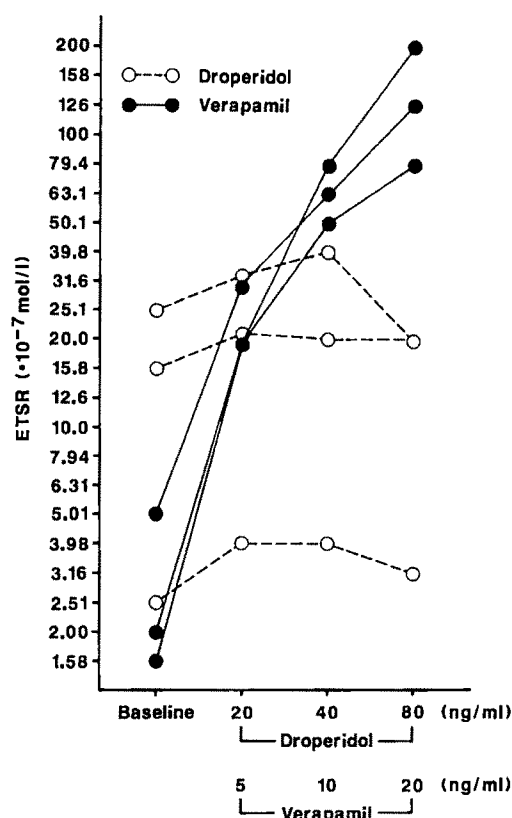


Figure 6. Epinephrine threshold for the development of slow responses (ETSR) at different concentrations of either droperidol (open circle, $n = 3$) or verapamil (closed circle, $n = 3$). Three sets of points for each drug indicate results obtained from individual preparations.

be responsible for both abnormal automaticity (13) and reentry (14). More importantly, a reentrant mechanism may underlie the arrhythmogenic interaction between halothane and epinephrine (4,15). Therefore, we predicted that, at least in part, the threshold for epinephrine-induced arrhythmias as well as the sensitivity of myocardium to epinephrine could be investigated using the ETSR as an indicator.

Halothane (2% and 4%) significantly increased the ETSR (Figure 2). This action of halothane is closely correlated with its direct action on slow calcium channels, i.e., calcium entry blocking action. Lynch et al. (16) reported that halothane depresses both the upstroke velocity and the contraction of slow responses in isolated, partially depolarized guinea pig papillary muscles. Ikemoto et al. (17) showed in the voltage-clamp experiments with single isolated rat ventricular cells that halothane reduces the slow inward current of the myocardium. In addition, our study showed that verapamil, like halothane, increases the ETSR in a dose-dependent manner (Figure 6). If these in vitro results are applicable to surgical patients, our findings are indicative of an

antiarrhythmic action rather than an arrhythmia-producing action of halothane, and several recent experiments suggest that this may be the case. First, in dogs, increasing the concentration of halothane from 1.25 to 2.0 MAC increased the doses of epinephrine required to produce ventricular arrhythmias (1). Second, halothane decreased the incidence of ventricular fibrillation in a canine model of acute occlusion/reperfusion arrhythmias (18). Third, in Purkinje fibers derived from infarcted canine hearts, halothane decreased the rate of spontaneous activity originating from the ischemic region (19). Fourth, halothane opposed formation of catecholamine-induced delayed after-depolarizations and triggered activity by altering intracellular calcium stores (20).

To investigate the influence of halothane on epinephrine/adrenoceptor interaction, we then studied the effects of selective α_1 - and β_1 -adrenergic receptor antagonists, alone or in combination with halothane, on the ETSR. α_1 -Blockade with either prazosin (Figure 3) or droperidol (Figure 6) did not alter the ETSR, whereas β_1 -blockade with metoprolol significantly increased the ETSR in a dose-dependent manner (Figure 4), suggesting that myocardial β_1 - rather than α_1 -adrenoceptors mediate most of the effects of epinephrine on the slow channel conductance. These results are consistent with the findings of Katz and Epstein (6) and Ehara et al. (9) that the β -actions of catecholamines on the myocardium cause an increase in the slow channel conductance. Our findings are also consistent with recent concepts regarding the membrane signaling mechanisms, which assume that β_1 -adrenergic stimulation activates slow calcium channels through an increased production of cyclic adenosine monophosphate and through subsequent activation of cyclic adenosine monophosphate-dependent protein kinase, whereas α_1 -adrenergic stimulation mainly results in the mobilization of calcium from intracellular vesicles by activating the phospholipase C/inositol 1,4,5 trisphosphate (IP_3) system (21-23).

The effects of prazosin and metoprolol on the ETSR were not influenced by halothane (Figure 5). If, as described above, the β_1 - rather than α_1 -actions of epinephrine on the myocardium cause an increase in the slow channel conductance, and accordingly if the ETSR mainly reflects epinephrine/ β_1 -adrenoceptor interaction, these results may suggest that halothane has no effect on the binding affinities of adrenoceptors, especially those of β_1 -adrenoceptors of the myocardium. Thus, halothane-induced significant increases in the ETSR (Figure 2) could not be ascribed to halothane/ β_1 -adrenoceptor interaction. These are consistent with Bernstein et al.'s data (24) that in a canine myocardial membrane preparation, halothane has no effect on either the affinity of β -adrenergic

receptors for [3H]dihydroalprenolol or *l*-isoproterenol, nor does it alter the number of available receptors at binding equilibrium.

In an in vitro experimental model, halothane increased the ETSR in a dose-dependent manner (Figure 2). As recent experimental findings indicate that the sensitivity of slow calcium channels to epinephrine reflects, at least in part, myocardial sensitivity to epinephrine (9), these results may suggest that halothane decreases rather than increases the sensitivity of myocardium to epinephrine. If halothane does not directly sensitize the myocardium to the arrhythmogenic properties of epinephrine, the arrhythmogenic interaction between halothane and epinephrine, observed in an in vivo state (1,2), might in part depend on their neural, metabolic, and hemodynamic mechanisms rather than direct actions on the myocardium. Atlee and Bosnjak (5) suggested that ventricular arrhythmias associated with halothane/epinephrine interaction are the result of the complex interplay of central neurogenic mechanisms. In addition, the data of Zink et al. (4), Hayashi et al. (25), and Hashimoto and Hashimoto (26) that epinephrine-induced increases in arterial blood pressure and/or heart rate played an important role in production of ventricular arrhythmias by epinephrine during halothane anesthesia suggest that the arrhythmogenic interaction of halothane and epinephrine might be mediated by the hemodynamic or metabolic mechanisms. On the other hand, our result showing that halothane has no effect on the binding affinities of β_1 -adrenoceptors of the myocardium may suggest that if halothane does sensitize the myocardium to the arrhythmogenic properties of epinephrine, the role of α_1 - rather than β_1 -adrenoceptors would predominate. The observations of Maze and Smith (3), Spiss et al. (7), and Maze et al. (8) that myocardial α_1 -adrenoceptors are responsible for the ventricular arrhythmogenic effects of epinephrine, and those of Freeman and Muir (27) that α_1 -adrenergic stimulation significantly slows the conduction of premature impulses in Purkinje fibers exposed to halothane, will support this.

The arrhythmogenic doses of epinephrine are different for different inhalation anesthetics such as halothane, enflurane, and isoflurane (2). Despite profuse studies, a clear understanding of the reason for this has not been realized. Reentrant excitation (4,15) rather than abnormal automaticity or triggered activity (20) has been invoked as an electrophysiologic mechanism for arrhythmogenic interaction between inhalation anesthetics and epinephrine. This form of reentry would be facilitated by abbreviation of the refractory period and by factors that slow conduction. Inhibition of active depolarization (decreased sodium current) and changes in passive membrane properties (increased internal longitudinal resistance) could lead

to decreased conduction velocity (10,28). Therefore, halothane's reduction of the epinephrine dose required to produce ventricular arrhythmias to a much greater extent than enflurane and isoflurane may suggest halothane's arrhythmogenic effects (the effects on refractory period, sodium channel conductance, and passive membrane properties) are greater and/or its antiarrhythmic effects (calcium entry blocking actions) are smaller than those of enflurane and isoflurane.

In conclusion, we found that halothane increases rather than decreases the ETSR in isolated partially depolarized myocardium. Any increase above the baseline ETSR after halothane administration could not be ascribed to halothane/adrenoceptor interaction but rather to the calcium entry blocking effects of halothane.

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Simultaneous Cardiac Output Measurements by Transtracheal Doppler, Electromagnetic Flow Meter, and Thermodilution During Various Hemodynamic States in Pigs

Sergio Gregoretti, MD, C.T. Henderson, BS, and E. L. Bradley, Jr., PhD

Departments of Anesthesiology and Biostatistics and Biomathematics, University of Alabama, Birmingham, Alabama

The transtracheal Doppler (TTD) method of cardiac output (CO) measurement was compared with thermodilution (TDL) and aortic electromagnetic flow meter (EFM). Simultaneous CO measurements with the three methods were obtained during various hemodynamic states in eight pigs. Cardiac output ranged from 1 to 3 L/min during the study. For 128 measurements, the mean difference \pm SD between TTD-TDL and TTD-EFM measurements was -0.037 ± 0.24 L/min and -0.055 ± 0.23 L/min, respectively. TDL-EFM mean difference \pm SD was -0.017 ± 0.15 L/min. The limits of the agreement between TTD

and the reference methods were 0.4 to -0.5 L/min. The limits of agreement between the reference methods were 0.3 to -0.3 L/min. Regression analysis yielded TTD = $0.383 + 0.779$ TDL ($r = 0.86$); TTD = $0.351 + 0.788$ EFM ($r = 0.87$); TDL = $0.077 + 0.95$ EFM ($r = 0.95$). Only a change >0.6 L/min in TTD CO could predict with 95% confidence a change in TDL or EFM CO. These results suggest that, in the CO range of this study, the TTD method does not accurately reproduce the CO measurements obtained by TDL or EFM.

(Anesth Analg 1991;73:455-9)

Transtracheal Doppler (TTD) is a new method of measuring cardiac output (CO) in which a Doppler transducer is mounted on the distal end of an endotracheal tube. An electronic unit drives the transducer and processes the Doppler ultrasound information to obtain the ascending aorta diameter and the blood velocity. Cardiac output is then computed from the cross-sectional area of the aorta and blood velocity (1). In the limited comparisons of TTD with established methods of CO measurement (2-5), no information is available on the accuracy of this new method during changes in hemodynamic variables such as heart rate, contractility, preload, and afterload, which may significantly modify the aortic diameter and/or blood velocity regardless of changes in CO (6). Insufficient data are available on the ability of the TTD method to track changes in CO, an essential requisite for any method that measures CO to gain wide clinical acceptance.

The present study was therefore performed to compare the TTD method of CO measurement with two established ones, thermodilution (TDL) and aortic electromagnetic flow meter (EFM), in the presence of broad changes in CO and/or other hemodynamic variables induced by different interventions.

Methods

Surgical Preparation

Eight miniature pigs weighing 22.1 ± 1.5 kg (mean \pm SD) were anesthetized with 30 mg/kg of intravenous pentobarbital and paralyzed with 0.25 mg/kg of intravenous metocurine. Endotracheal intubation was performed using a Doppler probe-tipped endotracheal tube. The lungs were mechanically ventilated at a rate of 12-16 breaths/min and a tidal volume of 10-15 mL/kg to maintain normocapnia. Anesthesia was maintained using 2-mg/kg increments of pentobarbital hourly. Cannulas were placed in the femoral vein and artery for fluid and drug administration, for pressure monitoring, and for blood sampling. The electrocardiogram (lead II) was continuously displayed. A 5F thermistor-tipped catheter (Spectramed, Oxnard, Calif.) was floated in the pulmonary artery

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Address correspondence to Dr. Gregoretti, Department of Anesthesiology, UAB, 619 South 19th Street, Birmingham, AL 35233

via the right internal jugular vein. A sternotomy was performed, the pericardium was opened, and an electromagnetic flow probe of appropriate size was placed around the aortic root, carefully avoiding obstruction of the vessel lumen. Snare were placed around the thoracic aorta and inferior vena cava to allow occlusion of these vessels. The pericardium was loosely closed with two stitches, the chest retractor was removed, and the sternum was left open. This study was approved by the institutional animal investigation committee.

Measurements

Thermodilution CO was measured using 3 mL of ice-cold saline as injectate and a Companion cardiac output computer (Gould, Oxnard, Calif.). Three measurements were made randomly with respect to the respiratory cycle 1 min apart and averaged. Any measurement differing by more than $\pm 10\%$ from the other two was discarded and a new measurement was obtained. Aortic blood flow was continuously measured with a factory-calibrated EFM (Cliniflow II, model FM701D, Carolina Medical Electronics, King, N.C.) positioned distal to the origin of the coronary arteries. Continuous TTD CO was obtained by using an Abcom cardiac output computer (Applied Biometrics, Eden Prairie, Minn.) that drives the Doppler transducer and processes the Doppler ultrasound information. We used in this study endotracheal Doppler tubes commercially available for human use (Applied Biometrics), modified only by adding length. These tubes have the Doppler transducer mounted on the tip in such a way that the ultrasonic beam intersects the aortic blood flow in humans at an angle of approximately 52° (2). Because of anatomic differences between pigs and humans, the actual angle of intersection of the ultrasonic beam with the aorta was determined in each pig as follows. After the sternotomy was performed, the internal diameter of the ascending aorta was calculated from the outer aortic diameter, measured using calipers, minus the aortic wall thickness, assumed to be 1.5 mm from preliminary observations in three pigs. The angle of intersection was then calculated from the measured aortic diameter and the velocity profile was obtained by the Abcom computer as described elsewhere (1). This angle was used for the remainder of the experiment to determine CO. Optimal position of the transtracheal Doppler probe was identified and maintained throughout the experiment by maximum intensity of the visual and audio representation of Doppler flow signals. At the end of the experiment, the animals were killed, the mediastinum was dissected, and the trachea was opened to verify the proper position of the Doppler probe with respect to

the aortic root. The ascending aorta was transected and the wall thickness was measured. In two pigs the measured aortic wall thickness was different from the assumed value and the CO was corrected accordingly.

The following hemodynamic variables were also measured: mean systemic and pulmonary arterial pressure, pulmonary artery wedge pressure, right atrial pressure, and heart rate.

The hemodynamic status was altered in each pig by the following nine interventions, each one lasting approximately 15 min: (1-4) infusion of isoproterenol, esmolol, phenylephrine, and sodium nitroprusside, respectively; (5) removal of 15 mL/kg of blood (hemorrhage); (6) infusion of 6% hetastarch in a volume equal to the blood removed (hemodilution); (7) reinfusion of the blood removed (hypervolemia); (8) cross-clamping of the thoracic aorta; (9) partial occlusion of the intrathoracic inferior vena cava. The hemodynamic values before each intervention were considered baseline values with the exception of interventions 6 and 7, in which the prehemorrhage values were considered as baseline. In each experiment there were, therefore, 16 stages (nine interventions and seven baselines). Simultaneous TTD, TDL, and EFM CO measurements were obtained at each stage. As TTD and EFM measurements were continuous whereas TDL were intermittent, TTD and EFM CO were expressed as the average of the values recorded from the beginning to the end of the TDL measurements (usually a 2-min time interval).

The agreement between the methods was analyzed according to Bland and Altman (7). The differences between simultaneous CO measurements obtained by two different methods were plotted against the average of the two measurements. The mean difference \pm SD between measurements and the limits of agreement, described by the mean difference \pm 2 SD, within which 95% of the differences will lie, was calculated. Cardiac output values obtained by the different methods were also compared using correlation and linear regression analysis. The trending capability of the TTD method was assessed by plotting the changes in TTD CO measurements between successive stages against the corresponding changes determined by TDL and EFM. In this plot, points that do not lie on the line of identity represent instances in which the change in CO measured by TTD was different from the change in CO measured by TDL or EFM. Comparison of hemodynamic variables among stages was performed using a repeated-measures analysis of variance.

Results

At the beginning of the experiments, mean \pm SD hemodynamic variables were as follows: TDL CO,

Table 1. Hemodynamic Changes During the Various Interventions^a

Variables	Interventions								
	ISO	ESMO	NEO	SNP	HEMORR	HEMODIL	HYPERVOL	AOCL	IVCOC
CO ^b	131 ± 22 ^c	79 ± 10 ^c	97 ± 15	74 ± 10 ^c	73 ± 7 ^c	176 ± 9 ^c	153 ± 13 ^c	105 ± 25	58 ± 14 ^c
HR	150 ± 27 ^c	79 ± 11 ^c	88 ± 14 ^c	112 ± 13 ^c	127 ± 18 ^c	100 ± 7	106 ± 12	97 ± 16	119 ± 16 ^c
MAP	85 ± 11 ^c	90 ± 11 ^d	166 ± 17 ^c	52 ± 9 ^c	66 ± 11 ^c	98 ± 3	94 ± 3	142 ± 14 ^c	81 ± 22 ^c
PAWP	81 ± 19	130 ± 22 ^c	210 ± 14 ^c	63 ± 8 ^c	51 ± 13 ^c	119 ± 18 ^c	150 ± 19 ^c	125 ± 16 ^c	54 ± 14 ^c
RAP	88 ± 26	130 ± 24 ^c	147 ± 27 ^c	75 ± 16 ^c	61 ± 7 ^c	117 ± 20	170 ± 40 ^c	109 ± 13	57 ± 15 ^c

ISO, isoproterenol; ESMO, esmolol; NEO, Neo-Syneprine; SNP, sodium nitroprusside; HEMORR, hemorrhage; HEMODIL, hemodilution; HYPERVOL, hypervolemia; AOCL, aortic cross-clamp; IVCOC, inferior vena cava occlusion; CO, cardiac output; HR, heart rate; MAP, mean arterial pressure; PAWP, pulmonary artery wedge pressure; RAP, right atrial pressure.

^aExpressed as percent ± SD of appropriate baseline. Baseline was the value before each intervention with the exception of hemorrhage and hypervolemia, in which case baseline was the prehemorrhage value.

^bCardiac output as measured by thermodilution.

^cP < 0.01 versus baseline.

^d0.01 < P < 0.05 versus baseline.

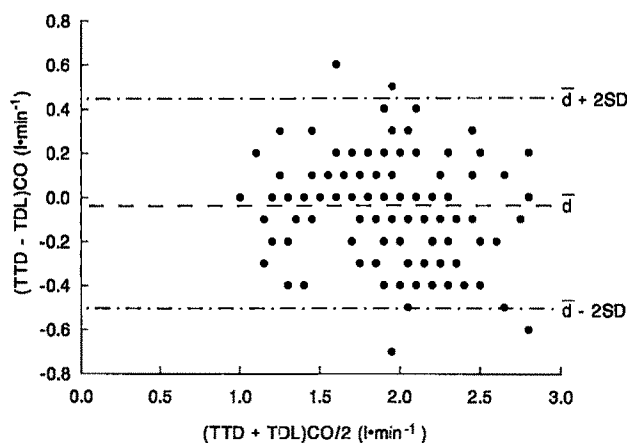


Figure 1. Agreement between TTD and TDL CO measurements analyzed according to reference 7. The difference between simultaneous TTD and TDL CO measurements ($[\text{TTD} - \text{TDL}] \text{CO}$) is plotted against the average of the two measurements ($(\text{TTD} + \text{TDL}) \text{CO}/2$). Identical values overlap. The broken line represents the mean difference ($\bar{d} = -0.037 \text{ L/min}$); the dash-dot lines represent the limits of agreement ($\bar{d} + 2 \text{ SD} = 0.4 \text{ L/min}$; $\bar{d} - 2 \text{ SD} = -0.5 \text{ L/min}$).

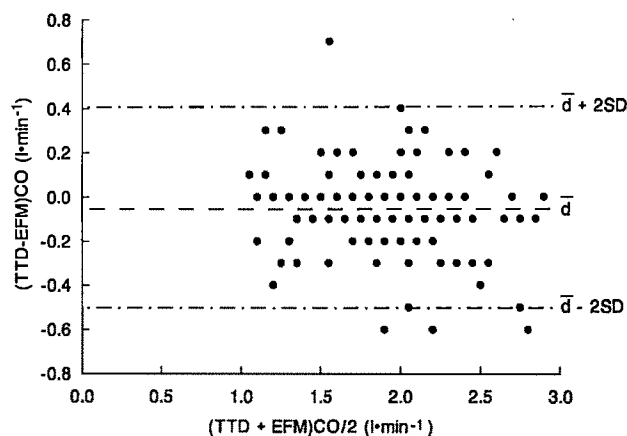


Figure 2. Agreement between TTD and EFM CO measurements analyzed according to reference 7. The difference between simultaneous TTD and EFM CO measurements ($[\text{TTD} - \text{EFM}] \text{CO}$) is plotted against the average of the two measurements ($(\text{TTD} + \text{EFM}) \text{CO}/2$). Identical values overlap. The broken line represents the mean difference ($\bar{d} = -0.055 \text{ L/min}$); the dash-dot lines represent the limits of agreement ($\bar{d} + 2 \text{ SD} = 0.4 \text{ L/min}$; $\bar{d} - 2 \text{ SD} = -0.5 \text{ L/min}$).

1.7 ± 0.3 L/min; heart rate, 114 ± 27 beats/min; mean systemic arterial pressure, 97 ± 7 mm Hg; mean pulmonary arterial pressure, 12 ± 2 mm Hg; pulmonary artery wedge pressure, 6 ± 1 mm Hg; right arterial pressure, 3 ± 1 mm Hg. Changes from baseline values during the various interventions are presented in Table 1. Cardiac output ranged from 1 to 3 L/min during the study.

The measurements from all pigs (128 data points) were combined and analyzed. The agreement between methods analyzed according to Bland and Altman (7) is presented in Figures 1-3. The mean difference ± SD between TTD-TDL and TTD-EFM CO measurements was $-0.037 \pm 0.24 \text{ L/min}$ and $-0.055 \pm 0.23 \text{ L/min}$, respectively. The mean difference ± SD between TDL and EFM measurements was $-0.017 \pm 0.15 \text{ L/min}$. The limits of agreement (mean difference ± 2 SD) between TTD and the reference

methods were 0.4 to -0.5 L/min , indicating that the TTD measurements may be as much as 0.4 L/min higher or 0.5 L/min lower than the simultaneous measurements obtained by TDL and EFM. The limits of agreement between TDL and EFM were 0.3 to -0.3 L/min . The plots of differences between simultaneous measurements against their average (Figures 1-3) did not reveal any relationship between measurement error and range of observed values.

Regression analysis yielded the following equations: $\text{TTD} = 0.383 + 0.779 \text{ TDL}$ ($r = 0.86$); $\text{TTD} = 0.351 + 0.788 \text{ EFM}$ ($r = 0.87$); $\text{TDL} = 0.077 + 0.95 \text{ EFM}$ ($r = 0.95$).

The changes in TTD CO between successive stages plotted against the corresponding changes as measured by TDL and EFM are presented in Figures 4 and 5. Of 125 changes, TTD CO changed in opposite directions to TDL CO in 10 instances, and to EFM CO

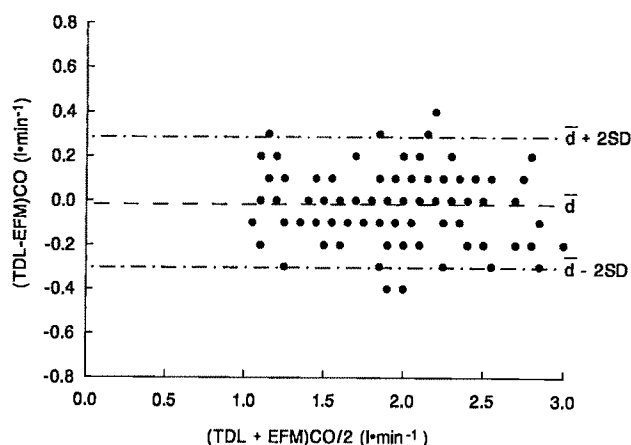


Figure 3. Agreement between TDL and EFM CO measurements. The difference between simultaneous TDL and EFM CO measurements $[(TDL - EFM) CO]$ is plotted against the average of the two measurements $[(TDL + EFM) CO/2]$. Identical values overlap. The broken line represents the mean difference ($\bar{d} = -0.017$ L/min); the dash-dot lines represent the limits of agreement ($\bar{d} + 2$ SD = 0.3 L/min; $\bar{d} - 2$ SD = -0.3 L/min).

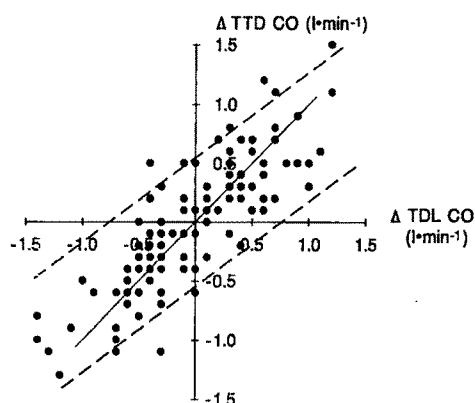


Figure 4. Changes in CO between successive stages measured by TTD (ΔTTD CO) compared with the changes measured by TDL (ΔTDL CO), with line of identity (solid line) and 95% confidence limits (broken lines). Identical values overlap.

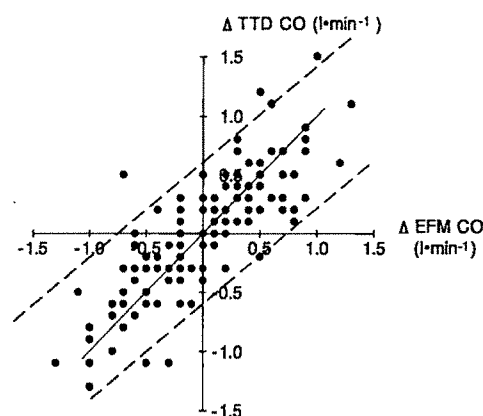


Figure 5. Changes in CO between successive stages measured by TTD (ΔTTD CO) compared with the changes measured by EFM (ΔEFM CO), with line of identity (solid line) and 95% confidence limits (broken lines). Identical values overlap.

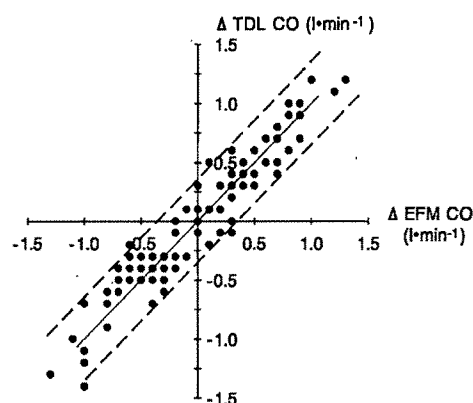


Figure 6. Changes in CO between successive stages measured by TDL (ΔTDL CO) compared with the changes measured by EFM (ΔEFM CO), with line of identity (solid line) and 95% confidence limits (broken lines). Identical values overlap.

in eight instances. Only changes in TTD CO larger than 0.6 L/min could predict a change in the same direction in TDL or EFM CO at a 95% confidence level. A plot of changes in TDL CO versus changes in EFM CO is presented in Figure 6. Thermodilution and EFM CO changed in opposite directions four times. Changes in TDL CO larger than 0.3 L/min were consistently associated with consensual changes in EFM CO.

Discussion

A comparison of a new measurement method with an established one aims to determine whether the methods agree well enough for the new to replace the old one. As there is no gold standard method to measure

CO, two established methods (TDL and EFM) were simultaneously used in this study. This design allows one to compare and contrast the agreement between TTD and TDL, and TTD and EFM, with the agreement between TDL and EFM measurements.

In this study, the overall agreement between the established methods was better than the agreement between the TTD method and the established ones. Although the new method correlated well with the old ones, the correlation TDL-EFM was the strongest. Analysis according to the methods of Bland and Altman (7) yielded an agreement within ± 0.3 L/min between the two standard methods, and within ± 0.5 L/min between TTD and standard methods. The mean difference between TTD-TDL and TTD-EFM measurements was close to zero, indicating that the TTD method did not have a consistent bias that could be adjusted to improve the agreement. Considering the CO range of 1-3 L/min examined in this

study, the agreement found between TTD and standard methods was quite poor. The trending capability of the TTD method was similarly poor, as only a relatively large change in TTD CO (0.6 L/min) could reliably predict a change in TDL or EFM CO. Our results cast doubt about the use of the method in patients with critically low CO or in a pediatric population. The accuracy of the TTD method at higher CO values, however, cannot be inferred from our results and should be further investigated.

The agreement found between TTD and the established methods is somewhat disappointing if two methodologic features of this study are considered. First, the optimal position of the TTD transducer was identified and carefully kept throughout the study by an experienced operator, thus making misalignments of the endotracheal tube with respect to the aorta an unlikely source of inaccurate measurements. Second, the actual aortic diameter was measured in each pig and the angle of incidence of the ultrasonic beam was calculated and fed into the computer for further calculations. Usually, the angle of incidence of the ultrasonic beam with the aortic blood flow is calculated empirically and assumed to be the same in every subject (2). Errors caused by a different angle of incidence of the ultrasonic signal with aortic flow owing to interindividual anatomic variability were therefore minimized. However, in addition to improper probe position and inaccurate aortic cross-sectional area determinations, several other theoretical and practical difficulties, extensively discussed elsewhere (6), are involved in the CO measurements

by Doppler velocimetry, which may explain the shortcomings of the TTD method tested.

In summary, the agreement of the TTD method with TDL or EFM was within ± 0.5 L/min. Only a change in TTD CO larger than 0.6 L/min could reliably predict a change in TDL or EFM CO. The results suggest that, in the CO range of 1-3 L/min, the TTD method does not accurately reproduce the CO measurement obtained by TDL or EFM.

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Clonidine Decreases Plasma Catecholamines and Improves Outcome From Incomplete Ischemia in the Rat

William E. Hoffman, PhD, Mary Ann Cheng, MD, Chinamma Thomas, MD, Verna L. Baughman, MD, and Ronald F. Albrecht, MD

Departments of Anesthesiology and Pathology, Humana/Michael Reese Hospital, University of Illinois, Chicago, Chicago, Illinois

Clonidine decreases central sympathetic activity and anesthetic requirement. We tested whether clonidine improves outcome from incomplete ischemia of the brain in rats. Control rats were anesthetized with $25 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ of intravenous fentanyl and inhalation of 70% nitrous oxide (N_2O). Clonidine-treated rats received fentanyl/ N_2O and $10 \mu\text{g}/\text{kg}$ of intravenous clonidine 10 min before ischemia, which was produced by right carotid ligation combined with hemorrhagic hypotension to 35 mm Hg for 30 min. Clonidine increased plasma glucose before ischemia and decreased blood catecholamine concentrations

during ischemia compared with the control group. Neurologic outcome was evaluated daily for 3 days after ischemia and histopathology was performed at the end of this period. Clonidine significantly improved neurologic outcome on each of the 3 days after ischemia. Histopathology was severe in the control group but not enough rats survived in this group for statistical analysis. The authors conclude that clonidine decreases sympathetic activity during ischemia and that this is associated with an improvement in outcome from incomplete ischemia.

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Ganglionic blockade decreases circulating catecholamines and improves neurologic outcome after incomplete cerebral ischemia in rats (1). Improved neurologic outcome was reversed by intravenous administration of norepinephrine and epinephrine infusion in ganglionic blocked rats, indicating that the effect was mediated by circulating catecholamines. Circulating catecholamines probably increased ischemic brain injury by stimulating central excitatory receptors (2) or by direct local damage (3). Clonidine, an α_2 -adrenoreceptor agonist, inhibits norepinephrine release during sympathetic activation (4) and during ischemia (5). In this study we evaluated whether clonidine may improve outcome from incomplete cerebral ischemia in rats.

Methods

These experiments were performed after institutional animal care committee approval had been obtained. Twenty-five male Sprague-Dawley rats (350-450 g) were anesthetized with isoflurane in a bell jar, tra-

cheally intubated, and mechanically ventilated with 1.4% isoflurane and 70% nitrous oxide (N_2O) in oxygen. The right femoral artery and left femoral vein were catheterized for arterial blood pressure recording, analysis of arterial blood gases, and drug administration. The right subclavian vein was catheterized for blood withdrawal. The right carotid artery was isolated for later clamping. Muscle paralysis was produced by an intravenous vecuronium infusion of $0.1 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Incisions were infiltrated with 0.5% bupivacaine. Isoflurane was withdrawn and inhalation of 70% N_2O was continued. Fentanyl was given as a $10\text{-}\mu\text{g}/\text{kg}$ bolus with an infusion of $25 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$.

In a preliminary study we tested the effect of $50 \mu\text{g}/\text{kg}$ of intravenous clonidine on outcome from ischemia. Four of five rats died due to hypertension-induced pulmonary edema. Therefore, we chose a lower dose of clonidine for this study ($10 \mu\text{g}/\text{kg}$). Two treatment groups were randomly tested: the control group ($n = 10$) received no pretreatment before ischemia; the clonidine group ($n = 10$) received a slow intravenous injection of clonidine ($10 \mu\text{g}/\text{kg}$) 10 min before ischemia.

Cerebral ischemia was produced by a combination of right carotid ligation and hemorrhagic hypotension to 35 mm Hg for 30 min. A range of 2 mm Hg was

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Address correspondence to Dr. Hoffman, Anesthesiology Department, Humana/Michael Reese Hospital, Chicago, IL 60616.

Table 1. Neurologic Scoring^a

Consciousness	Walking
0 = Normal	0 = Normal
1 = Restless	1 = Paw adduction
2 = Lethargic	2 = Hypomobility
3 = Stuporous	3 = Circling to stroke side
4 = Seizures	4 = Unable to stand
5 = Death	
Rope platform	Rotating screen
0 = Climbs to platform	0 = Grasps to 180° >5 s
1 = Pulls up rear legs	1 = Grasps to 180° <5 s
2 = Hangs on 5 s	2 = Grasps to 90°, not 180°
3 = Hangs on <5 s	3 = Falls from vertical screen
4 = No grasp reflex	
Limb tone	Pain reflex
0 = Normal	0 = Normal
1 = Weak	1 = Hypoactive

^aTotal score = 18.

allowed for the target pressure. Arterial carbon dioxide tension was maintained at 35–40 mm Hg by adjusting ventilation and pH_a at 7.40 with a bicarbonate infusion during this period. Rectal and skull temperatures were measured using thermistor probes and maintained at 37°C using an overhead heat lamp. At the end of ischemia, the carotid artery was unclamped and the withdrawn blood was reinfused over 10 min. All catheters were removed, incisions were closed, the anesthetic was withdrawn, and the trachea was extubated 30 min after the end of ischemia. Rectal temperature was monitored for 3 h after recovery in two rats from each group to evaluate maintenance of normothermia.

Neurologic outcome was scored in each rat every 24 h for 3 days, starting 24 h after ischemia. Neurologic deficits were scored in consciousness, walking, motor performance tasks, limb tone, and response to painful stimuli (Table 1). Scores ranged from 0 (normal) to 18 (stroke-related death). Stroke-related death was scored after a minimum of 3 h postischemia only if the rats showed progressive signs of stroke impairment.

Brain histopathology was evaluated in rats that survived the 3-day neurologic scoring period. The rats were anesthetized with isoflurane in a bell jar and killed by a transcardial perfusion of 20 mL of saline followed by 20 mL of 10% buffered formalin. The brain was removed and stored in 10% formalin for 1 wk. Coronal sections were cut and embedded in paraffin. Brain slices (7 μm) were mounted on glass slides and stained with hematoxylin and eosin. The sections were evaluated in a blinded manner by a neuropathologist. The caudate nucleus and hippocampus (CA1–CA4) are sensitive to ischemic injury in

this model of ischemia. Separate coronal sections containing these regions were used for histologic examination. The section containing the caudate was scored as follows: 0 = no damage, 1 = scattered neuronal damage, 2 = small infarcts, 3 = infarcts involving 50% of the ischemic caudate, 4 = infarcts involving 50% of the ischemic hemisphere, 5 = total hemisphere infarct. A section containing the hippocampus was scored as follows: 0 = no damage, 1 = 50% injury of hippocampal pyramidal cells, 2 = 100% injury of hippocampal pyramidal cells, 3 = 50% ischemic hemisphere infarct, 4 = 100% hemisphere infarct.

Data are reported as mean \pm SE. Nonparametric data, including neurologic outcome, and histopathologic data were compared between groups using Kruskal-Wallis tests. Correlation between neurologic outcome and histopathology was evaluated using a Spearman rank order correlation. Physiologic data were evaluated using two-way analysis of variance and Tukey tests for post hoc comparisons.

Results

Clonidine produced a brief increase in arterial blood pressure followed by a decrease at the end of the control period (Table 2). Clonidine produced an increase in plasma glucose before ischemia compared with the control group. Plasma glucose increased in both groups during the ischemic challenge. Plasma catecholamines were significantly decreased during ischemia in clonidine-treated compared with control rats (Figure 1). Rectal temperature was measured for 3 h after ischemia in two rats from each group. Rectal temperature decreased from 37° to 36°C within 30 min and returned to 37°C within 1 h in both groups.

Neurologic outcome was better in clonidine-treated than in control rats (Figure 2). This difference was significant on each of the 3 days of neurologic examination ($P < 0.05$). Histopathology was severe in the five control rats that survived for 3 days after ischemia (Figure 3). Their scores were not significantly different from clonidine-treated rats ($P = 0.14$). The correlation between neurologic outcome and histopathology in all rats was $r = 0.423$, $P < 0.05$.

Discussion

We found that intravenous clonidine produced an initial increase followed by a decrease in arterial blood pressure. The increase is mediated by clonidine-induced α_1 - and α_2 -adrenoreceptor stimulation of arterial smooth muscle. This limited the dose of clonidine we were able to test as higher doses (50 $\mu\text{g/kg}$) produced prolonged hypertension and pulmonary edema. Within 10 min of injection, cloni-

Table 2. Mean Arterial Pressure, Blood Gas Tensions, pH_a, and Plasma Glucose

Group treatment	MAP (mm Hg)	Paco ₂ (mm Hg)	Pao ₂ (mm Hg)	pH _a	Plasma glucose (mg/dL)
Control (n = 10)					
Baseline	135 ± 5	38.4 ± 0.9	138 ± 4	7.41 ± 0.01	176 ± 6
Ischemia (15)	35 ± 1 ^a	36.6 ± 1.2	156 ± 2	7.37 ± 0.02	
Ischemia (30)	35 ± 1 ^a	38.0 ± 0.9	151 ± 4	7.39 ± 0.01	325 ± 29 ^a
Recovery	114 ± 5	41.1 ± 1.0	134 ± 6	7.38 ± 0.01	177 ± 22
Clonidine (n = 10)					
Baseline	82 ± 4 ^b	39.0 ± 0.8	145 ± 4	7.40 ± 0.01	232 ± 8 ^b
Ischemia (15)	35 ± 1 ^a	37.4 ± 0.7	153 ± 2	7.38 ± 0.01	
Ischemia (30)	35 ± 1 ^a	37.7 ± 0.7	153 ± 3	7.39 ± 0.01	308 ± 21 ^a
Recovery	106 ± 4	38.6 ± 0.6	142 ± 7	7.40 ± 0.01	226 ± 17

MAP, mean arterial pressure; Paco₂, arterial CO₂ tension; Pao₂, arterial O₂ tension.

Data reported as mean ± SE. Numbers in parentheses indicate minutes of ischemia.

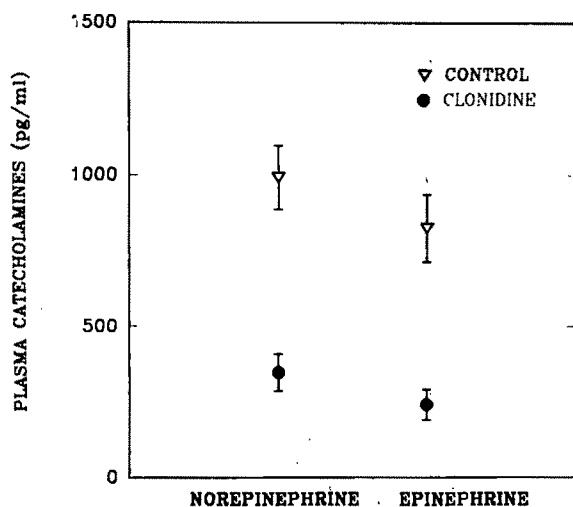
^aP < 0.05 compared with baseline.^bP < 0.05 compared with control.

Figure 1. Plasma catecholamines during ischemia (mean ± SE). Catecholamines were measured at the end of the ischemic period in each rat. Both norepinephrine and epinephrine were significantly different between clonidine and control treatment groups ($P < 0.05$).

dine (10 μ g/kg) produced significant hypotension. In addition, plasma catecholamine concentrations were decreased in clonidine-treated rats during ischemia. This is consistent with previous reports that clonidine decreases central sympathetic activity by stimulation of brain α_2 -adrenoreceptors (4,6). Although the pretreatment interval was only 10 min in these studies, the prolonged half-life of clonidine (8–12 h) suggests that it would be effective for an extended period. Neurologic outcome was significantly improved in clonidine-treated compared with control rats. Our results suggest that clonidine improved ischemic outcome by decreasing sympathetic activity.

Brain ischemia is associated with elevated central and peripheral sympathetic activity. Globus et al. (7)

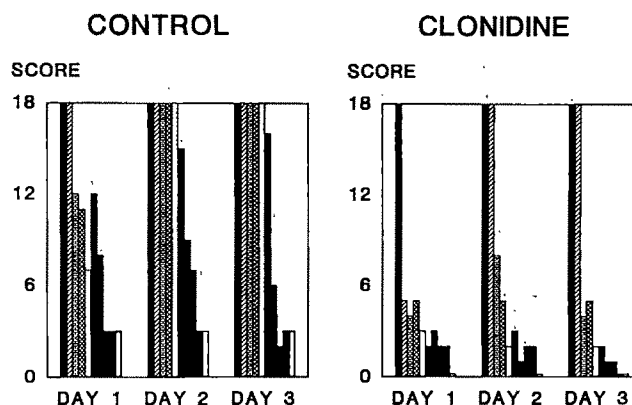


Figure 2. Total neurologic score for the 3-day scoring period. Each bar represents daily score for each individual rat. Neurologic score was significantly better in clonidine-treated compared with control rats on all 3 days ($P < 0.05$).

measured extracellular norepinephrine in rat hippocampus by tissue perfusion and reported that fore-brain ischemia increased catecholamine release. Weinberger and Nieves-Rosa (8) studied gerbil synaptosomes and saw increased release of norepinephrine during ischemia. After ischemia, norepinephrine release was decreased but synaptosome norepinephrine uptake was inhibited. They suggested that direct toxic effects of ischemia were responsible for alterations in release and uptake of catecholamines. Meyer et al. (9) reported increased cerebrospinal fluid norepinephrine concentrations in patients with stroke. They suggested that cerebrospinal fluid catecholamines may increase after ischemia because of blood-brain barrier breakdown.

There is controversy regarding the influence of sympathetic activity on outcome from ischemia. Ganglionic blockade or interruption of central sympathetic activity increases hippocampal neuronal injury

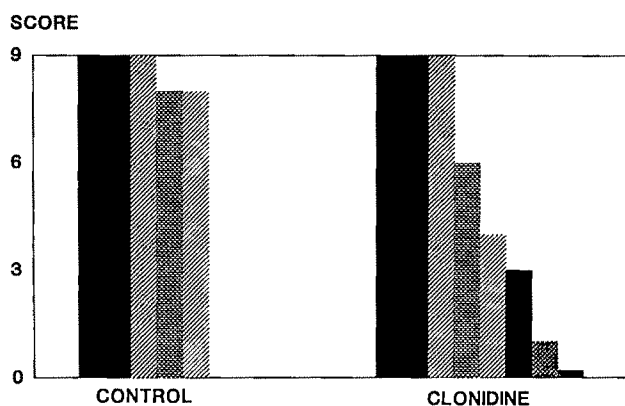


Figure 3. Histopathologic score in rats that survived 3 days after ischemia. Scores represent total histopathologic score for each individual rat measured in caudate and hippocampal sections. Scores were not different between treatment groups ($P = 0.14$). No neuronal damage was seen in nonischemic tissues.

produced by near complete ischemia in rats (10,11). However, others have shown that disruption or depletion of central sympathetic activity enhances recovery from ischemia and decreases neuronal injury (12,13). We found that ganglionic blockade improves outcome from incomplete ischemia and that this effect is dependent on a decrease in plasma catecholamine concentration (1). The reason for the controversy over whether catecholamines improve or worsen ischemic outcome is unclear. Perhaps central catecholamine stimulation worsens outcome during incomplete ischemia by stimulating central excitatory mechanisms (3). This may not be important during complete or near-complete ischemia because neurons are inactive. On the other hand, stimulation of sympathetic activity after ischemia with α_2 -adrenoreceptor antagonists may decrease neuronal injury by different mechanisms (14).

There is little clinical data available concerning stroke outcome with clonidine treatment. Clonidine has been used to treat hypertension and to decrease afterload in congestive heart failure and aortic surgery (15-17). Plasma catecholamines are decreased and circulatory stability is improved with clonidine. Clonidine has been shown to decrease cardiac output and cerebral blood flow in hypertensive patients (15). However, we are not aware of a study evaluating clonidine treatment and stroke outcome.

Clonidine may decrease body temperature in association with its ability to inhibit sympathetic tone (18). Postischemic hypothermia to 31°C for 1 h improves outcome from incomplete ischemia in rats (19). Perhaps this is a mechanism of neuronal protection with clonidine. However, we saw only a modest decrease in body temperature after ischemia (-1°C) and no difference between control and clonidine-treated rats. This indicates that postischemic temperature changes

did not mediate the improved outcome seen here with clonidine.

Plasma glucose was increased by clonidine treatment before ischemia. This effect is probably produced by α_2 -adrenoreceptor-induced inhibition of insulin release (20). In this model of incomplete cerebral ischemia, increased plasma glucose before and during ischemia worsens outcome from ischemia (21). As the clonidine-treated group had higher plasma glucose but a better outcome from ischemia, plasma glucose was probably not an important factor determining outcome in this study.

We were unable to use a second dose of clonidine (50 $\mu\text{g/kg}$) in this study because it produced hypertension above 150 mm Hg for several minutes. This resulted in pulmonary edema, hypoxia, and a poor recovery in the rats. A dose-response curve for clonidine and ischemic outcome would indicate whether 10 $\mu\text{g/kg}$ of clonidine represents a maximum brain protective effect for α_2 -adrenoreceptor stimulation. In other experiments we have tested a more specific α_2 -adrenoreceptor agonist, dexmedetomidine (22). Dexmedetomidine produced similar responses as clonidine but was more effective in decreasing ischemic injury. This suggests that 10 $\mu\text{g/kg}$ of clonidine did not produce a maximum ischemic protective effect. This may be due to an inadequate drug dose or due to the fact that clonidine is not a full agonist of α_2 -adrenoreceptors and stimulates α_1 -adrenoreceptors as well (23).

In conclusion, clonidine produced a decrease in plasma catecholamines during ischemia and improved neurologic outcome from incomplete ischemia in spite of an elevation in plasma glucose. These results are consistent with reports that sympathetic activity worsens ischemic outcome and clonidine attenuates this effect.

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Administration of Inhaled Anesthesia With High-Frequency Oscillation: An In Vitro Study

Marc R. Raffe, DVM, MS, and Annette LeDuc, BS

Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, Minnesota

To assess administration of inhaled anesthesia during high-frequency oscillation, we evaluated the performance of a high-frequency oscillator that permitted incorporation of a precision vaporizer. The ventilator design used a single gas source for both vaporizer circuit and ventilatory support. The performance was evaluated in conjunction with a test lung device. The vaporizer performance was accurate when high-frequency, low-volume gas flow was used to

provide source gas for the vaporizer. The ventilator provided accurate halothane delivery to the test lung device. Based on the results of this study, inhaled anesthesia can be accurately administered in conjunction with high-frequency oscillation. A single gas source that transverses the vaporizer before breathing circuit entrainment is critical for accurate results.

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High-frequency ventilation is used for acute respiratory disease syndromes that are unresponsive to conventional techniques of ventilatory support (1). Although high-frequency ventilation is used in critical care, its role in anesthesia for surgery remains less defined. High-frequency ventilation is advantageous in cases that involve large air leaks from the respiratory tract, high-grade parenchymal disease, or require stable surgical fields (2,3). Most of these reports use injectable anesthetic techniques and use high-frequency ventilation as the principal model of ventilatory support. No information exists regarding incorporation of inhaled anesthetics for anesthetic delivery as a primary or adjunctive technique during high-frequency oscillation (4). The purpose of this study is to determine the effect of pulsatile gas flow on vaporizer accuracy and to determine whether inhaled anesthetics can be administered through a high-frequency oscillator.

Materials and Methods

The ventilator used in this study was a variable-speed piston, high-frequency oscillator (model 320 Y, Tres

Tec Corp., San Antonio, Tex.) that was adapted for a precision vaporizer in the primary breathing circuit. The gas flow for the vaporizer was incorporated upstream of the oscillator module and provided the gas source for the patient delivery circuit (Figure 1). Preliminary studies indicated that the 2.75-L/min gas flow through the vaporizer circuit was constant at all ventilator frequencies.

A freshly serviced halothane vaporizer (Fluotec III, Fraser-Harlake Corp., Orchard Park, N.Y.) was attached to a calibrated flowmeter, and the concentration output was calibrated at 2.75 L/min across a range of 0%–3% halothane (Ayerst Inc., New York, N.Y.) in 0.5% increments. Gas samples were collected after a 5-min equilibration period and were analyzed using an infrared spectrophotometer device (Sensormedics LB-2, Anaheim, Calif.) that was calibrated with primary halothane standard gases. For each trial, gas samples were collected in triplicate and were averaged for a single data point.

To evaluate the accuracy of the vaporizer performance during high-frequency oscillation, the vaporizer output was analyzed in the range of 10–42 Hz. Vaporizer output was analyzed in 1% increments between 1% and 3% halothane as indicated by the dial setting. The values obtained were compared with the standard calibration curve generated by continuous gas flow.

The effect of the breathing circuit on delivered gas concentration was also studied. A modified Mapleson A breathing circuit is integrally incorporated in

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Address correspondence to Dr. Raffe, Department of Small Animal Clinical Sciences, College of Veterinary Medicine, University of Minnesota, St. Paul, MN 55108.

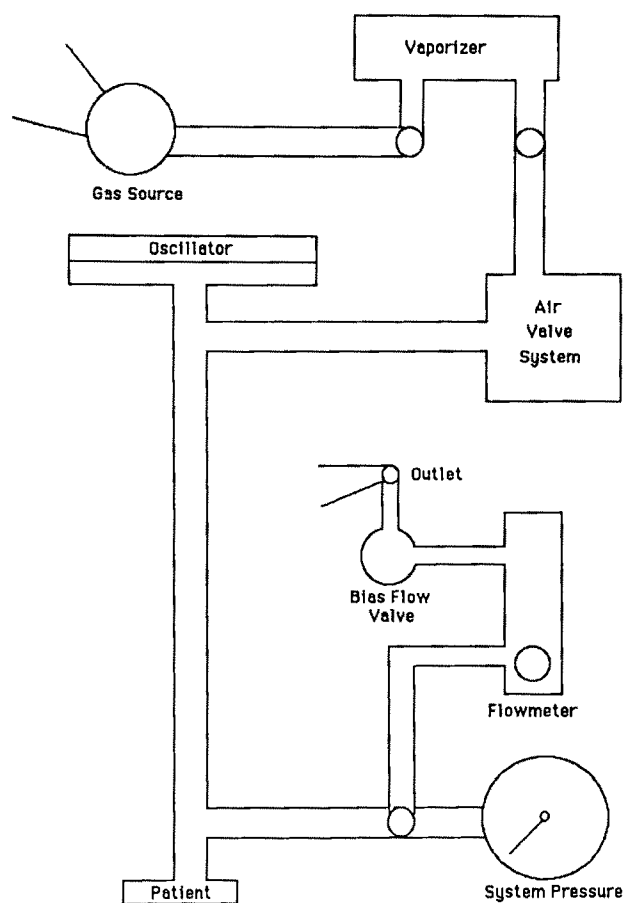


Figure 1. Schematic diagram of the high-frequency oscillator device with the vaporizer interfaced downstream of the gas source and upstream of the oscillator circuit.

the ventilator. An adiabatic test lung (Bird Corp., Sand Point, Idaho) was attached at the patient interface. A sampling site was interfaced so that gas samples were collected within the lung for analysis of halothane concentration. For all trials, inspiratory time was standardized at 30% of ventilatory cycle. A bias port gas flow rate of 2.7 L/min was necessary to minimize positive end expiratory pressure in the breathing circuit. The performance was evaluated in the frequency range of 10–42 Hz. Five-minute intervals were permitted after vaporizer or frequency changes to allow the gas concentration in the breathing circuit to stabilize. Gas samples from the outlet port of the vaporizer and the bias gas flow port were simultaneously collected and analyzed. All analyses were performed in triplicate and were averaged for a single data point.

The data in all experiments were analyzed using two-way analysis of variance, with a significance level of $P < 0.05$. Regression coefficients were calculated by comparing vaporizer output at constant and

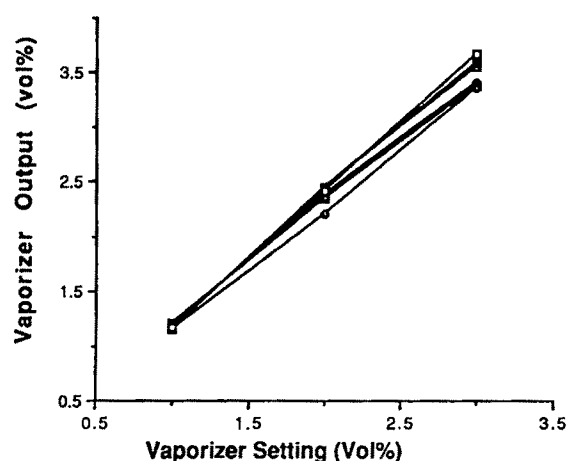


Figure 2. Comparison of vaporizer performance under pulsatile gas flow with constant gas flow from 10 to 25 Hz. —□—, 10 Hz; —◆—, 14 Hz; —■—, 18 Hz; —◇—, 21 Hz; —■—, 25 Hz; —□—, constant flow.

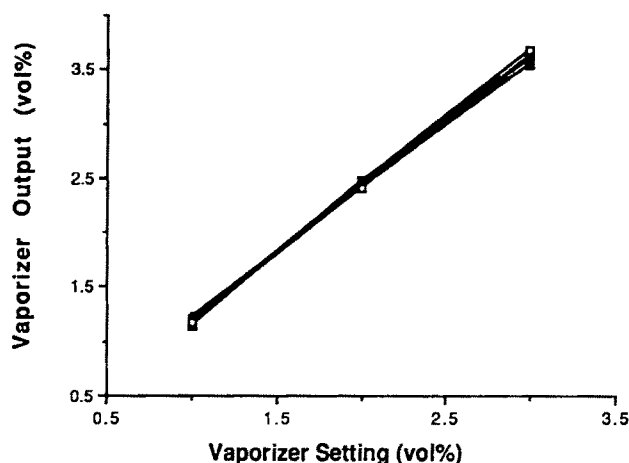


Figure 3. Comparison of vaporizer performance under pulsatile gas flow with constant gas flow from 28 to 42 Hz. —□—, 28 Hz; —◆—, 30 Hz; —■—, 35 Hz; —◇—, 40 Hz; —■—, 42 Hz; —□—, constant flow.

pulsatile gas flow and by comparing vaporizer output with breathing circuit concentration.

Results

The comparisons of vaporizer performance for pulsatile gas flows and constant gas flows are shown in Figures 2 and 3 and Table 1. There was no significant difference in vaporizer performance at any ventilator frequency or at any halothane concentration when compared with constant flow values. Because of the consistency of response for all frequencies evaluated, all data points were pooled and collectively analyzed. A regression coefficient of $r = 0.97$ was calculated for this data group.

The comparison of anesthetic delivery circuit concentration with vaporizer output is shown in Figures

Table 1. Vaporizer Output and Circuit Concentration During High-Frequency Oscillation

Vaporizer setting (%/%)	Ventilator frequency (HZ)	Mean vaporizer output (%/%)	Standard deviation	Mean circuit concentration (%/%)	Standard deviation
1	Constant flow	1.17	0.11	NM	NM
2	Constant flow	2.42	0.16	NM	NM
3	Constant flow	3.49	0.10	NM	NM
1	10	1.15	0.03	0.94	0.06
2	10	2.45	0.22	1.95	0.14
3	10	3.57	0.25	2.87	0.36
1	14	1.19	0.04	1.13	0.18
2	14	2.39	0.06	2.09	0.30
3	14	3.43	0.10	2.95	0.41
1	18	1.21	0.02	1.04	0.01
2	18	2.36	0.05	1.93	0.10
3	18	3.39	0.07	2.66	0.18
1	21	1.15	0.02	1.11	0.07
2	21	2.21	0.07	2.15	0.11
3	21	3.37	0.04	3.16	0.09
1	25	1.16	0.10	1.23	0.12
2	25	2.46	0.13	2.24	0.1
3	25	3.61	0.17	3.31	0.12
1	28	1.18	0.05	1.21	0.19
2	28	2.42	0.06	2.26	0.06
3	28	3.55	0.01	3.25	0.10
1	30	1.23	0.03	1.23	0.14
2	30	2.41	0.01	2.23	0.05
3	30	3.63	0.05	3.29	0.08
1	35	1.14	0.05	1.24	0.17
2	35	2.48	0.01	2.12	0.27
3	35	3.55	0.11	2.95	0.46
1	40	1.20	0.04	0.98	0.2
2	40	2.46	0.03	1.96	0.54
3	40	3.69	0.05	2.79	0.85
1	42	1.18	0.05	1.01	0.32
2	42	2.45	0.04	1.92	0.67
3	42	3.60	0.14	2.71	0.91

NM, not measured.

4 and 5 and Table 1. There were no significant differences noted when the circuit concentration was compared with the vaporizer output at any concentration. Because of the consistency of response for all frequencies evaluated, all data points were pooled and collectively analyzed. A regression coefficient of $r = 0.89$ was calculated for this data group.

Discussion

No information exists regarding vaporizer performance characteristics when used with high-frequency oscillation. The vaporizer used in this study

has been reported to be unaffected by pressure fluctuations originating in the breathing circuit (5). However, the effect of pulsatile carrier gas characteristics on vaporizer performance has not been previously described. In our study, all other factors that may affect vaporizer performance were standardized to limit their effect on vaporizer performance. The inlet flow of 2.7 L/min is within the carrier gas flow range reported to produce accurate performance characteristics for the Fluotec III vaporizer (5). All trials were performed in a thermostable area maintained within 1°C for the entire experiment. The halothane manufacturer and source was the same for all trials. The results indicate that accurate vaporizer performance

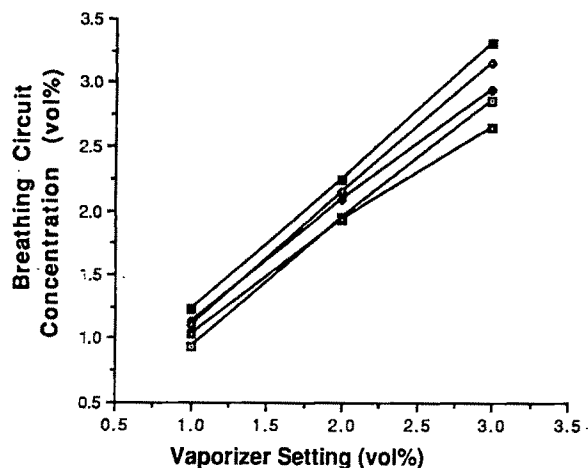


Figure 4. Comparison of breathing circuit concentration at the test lung with vaporizer output from 10 to 25 Hz. \square -, 10 Hz; \blacklozenge -, 14 Hz; \blacksquare -, 18 Hz; \blacklozenge -, 21 Hz; \blacksquare -, 25 Hz.

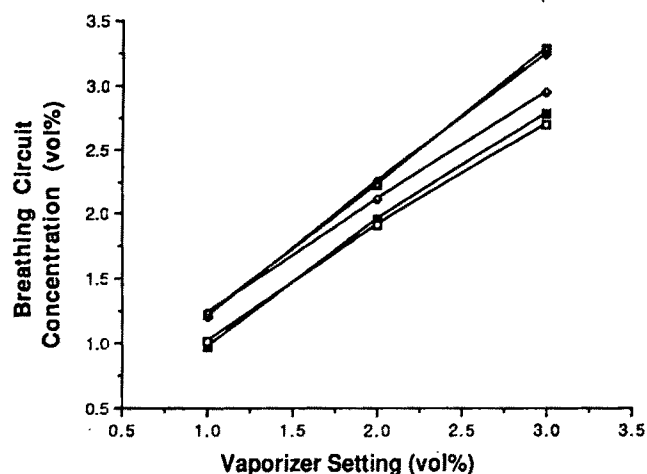


Figure 5. Comparison of breathing circuit concentration at the test lung with vaporizer output from 28 to 42 Hz. \blacklozenge -, 28 Hz; \blacksquare -, 30 Hz; \blacklozenge -, 35 Hz; \blacksquare -, 40 Hz; \square -, 42 Hz.

can be expected during high-frequency, low-volume gas flow through the vaporizer. We believe that a reason for the accurate vaporizer performance is that the characteristics of rapid, pulsatile gas flow approximate continuous flow through the vaporizer chamber. Although we did not evaluate enflurane and isoflurane delivery characteristics in the study, vaporizer performance has been shown to be linked to internal design characteristics (5). Therefore, delivery of isoflurane and enflurane by a vaporizer based on similar principles should produce results similar to those of the current study.

The issue of circuit design and implication on deliv-

ered agent concentration is also critical. Many high-frequency ventilator circuit designs use entrainment techniques to augment gas flow (1). The injection of a pressurized gas source into the breathing circuit is augmented by gas entrained in proximity to the pressure source. Entrained gas may originate from external sources such as conditioned humidified gases or from direct entrainment into the ventilator circuit from ambient gas sources. This dual gas source poses a potential problem in the accurate delivery of inhaled anesthesia (4). High-pressure gas sources that route through the vaporizer are unsuitable because commercially available vaporizers are not designed to work under high-pressure conditions. Supplemental gas entrainment in the breathing circuit may dilute delivered anesthetic concentration. Thus, inhaled anesthetic delivery with high-frequency ventilators requires either a single gas source that contains the anesthetic or the capacity to admix several gas sources in appropriate concentrations to produce the final delivered concentration (4). The ventilator used in this study uses a single gas source introduced through the vaporizer circuit and subsequently delivered by the ventilator module and patient delivery circuit (Figure 5). Unlike other systems, the patient breathing circuit is designed to administer the gas mixture processed through the ventilator circuit (i.e., inhaled anesthesia) without gas dilution by additional entrainment. This permits a constant anesthetic concentration to the delivery circuit that results in an accurate inspired concentration of an anesthetic.

In summary, inhaled anesthesia can be administered with an appropriately designed high-frequency ventilator provided that the ventilator design incorporates a single gas source unit that prevents or minimizes gas dilution, introduces the anesthetic upstream of the ventilator unit, and minimizes supplemental gas entrainment in the anesthetic breathing circuit. Vaporizer performance does not appear to be altered by using source gases that have high-frequency, low-pressure characteristics that approximate continuous gas flow through the vaporizer chamber.

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Intradermal Anesthesia and Comparison of Intravenous Catheter Gauge

Raphael Y. Gershon, MD, BettyLou K. Mokriski, MD, and M. Jane Matjasko, MD

Department of Anesthesiology, University of Maryland Medical School, Baltimore, Maryland

A double-blinded randomized prospective study was performed to determine whether alkalinization of lidocaine decreases the pain of intradermal injection and if a larger intravenous catheter (16 gauge) causes more discomfort on insertion than a smaller (20 gauge) catheter when intradermal anesthesia has been used. In a random manner, 100 patients received skin wheals with commercially prepared lidocaine or lidocaine with the addition of sodium bicarbonate before the insertion of a 16- or 20-gauge intravenous catheter. Visual analogue pain scores were obtained after the skin wheal was placed and after the intravenous catheter was inserted. There

was no statistically significant difference in pain scores between the two local anesthetic solutions. However, the catheter insertion pain scores were slightly, but statistically significantly larger in the 16-gauge group regardless of local anesthetic solution used. The addition of sodium bicarbonate to commercially prepared lidocaine does not decrease the pain associated with an intradermal skin wheal. There is a slight increase in patient discomfort upon insertion of a large-bore intravenous catheter, even with the prior use of local anesthetic.

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Intradermal anesthesia, commonly used to provide analgesia for intravenous catheter insertion, may itself be painful (1,2). There may be a relationship between pain induced by the administration of lidocaine and the pH of this local anesthetic solution (3,4). Furthermore, the efficiency of the intradermal analgesia in attenuating needle stick pain has not been studied in the clinical setting.

A large-bore intravenous catheter is often desirable for optimal patient care. However, there is concern that patient discomfort on insertion is significantly greater, even with use of a local anesthetic. We performed a double-blinded randomized prospective study to determine (a) whether alkalinization of lidocaine decreases the pain of intradermal injection, and (b) whether a larger intravenous catheter (16 gauge) causes more discomfort on insertion than a smaller (20 gauge) catheter when intradermal anesthesia has been used.

Methods

One hundred healthy patients (ASA physical status I and II) gave their consent to participate in this approved study. They were randomized to receive 0.25 mL of intradermal anesthesia with either lidocaine plain ($n = 50$) or lidocaine adjusted to a pH of 7.3 with sodium bicarbonate ($n = 50$). The preparations were made by adding sodium bicarbonate (8.4%) or preservative-free sterile water to commercially prepared preservative-free 1.0% lidocaine in a 1:2 ratio with resultant 0.67% lidocaine with a pH of 7.3 or 6.4, respectively. The pH values were measured on a Nova Stat Profile #5 (Nova Biomedical, Boston, Mass.).

All intradermal anesthesia was administered with a 25-gauge needle and tuberculin syringe. Injection was performed over a 5-s period to the back of the patient's hand ($n = 95$) or forearm ($n = 5$) by the same investigator after the skin was cleansed with 70% isopropyl alcohol and allowed to dry. The investigator was blinded to the anesthetic. The same investigator then randomly inserted either a 16-gauge ($n = 52$) or 20-gauge ($n = 48$) intravenous catheter within 15 s after performance of the skin wheal in the usual manner. The skin wheal was placed directly over a vessel, which allowed immediate vessel penetration after catheter passage through the wheal.

A visual analogue pain score (VAPS) was recorded

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Address correspondence to Dr. Gershon, Department of Anesthesiology, Emory University School of Medicine, c/o Grady Memorial Hospital, 69 Butler Street, S.E., Atlanta, GA 30303.

Table 1. Visual Analogue Scores After Intradermal Anesthesia

Local anesthetic	Mean	Range
Lidocaine plain	1.24	0-5.00
Lidocaine and bicarbonate	0.81	0-4.50

$P > 0.05$. There is no statistically significant difference between mean values.

Table 2. Visual Analogue Scores After Intravenous Insertion

Local anesthetic	20 Gauge		16 Gauge	
	Mean	Range	Mean	Range
Lidocaine plain	0.61	0-2.2	1.22	0-5.4
Lidocaine and bicarbonate	0.56	0-3.0	0.97	0-4.0

$P > 0.05$. There is no statistically significant difference between mean values within each gauge group.

after intradermal anesthesia and again after catheter insertion using a 10-cm linear analogue pain scale. Subjects were instructed to score a pain-free injection as zero and the worst pain imaginable as 10. Markings on the analogue pain scale were measured to the nearest millimeter.

Data were subjected to analysis of variance or Wilcoxon test as appropriate. A P value less than 0.05 was considered significant.

Results

No differences were found among the four groups in terms of age, race, sex, or site of insertion. No statistically significant difference was found between plain and alkalized lidocaine after intradermal anesthesia (Table 1). No statistically significant difference was found between plain and alkalized lidocaine after intravenous line insertion (Table 2). A statistically significant difference was found between 16- and 20-gauge catheter insertion: mean pain scores were 1.09 and 0.58, respectively ($P < 0.05$).

Discussion

Our results do not confirm a previous report that pain on intradermal injection of lidocaine is diminished by the addition of bicarbonate (3). In contrast to prior studies, we studied more patients (100 vs 24) in an actual clinical setting as opposed to volunteers (1-3). The clinician generally raises a skin wheal to ameliorate the ensuing pain of an inserted catheter. Our data are relevant to the clinical situation because intravenous catheters were actually inserted through the skin wheals, and VAPS were taken both imme-

diately after performance of the skin wheal and again after catheter insertion. Although there should be no correlation between skin wheal pain and catheter insertion, prior studies (3,4) did not test the efficiency of the skin wheal for catheter insertion.

Lidocaine skin wheal pain has been reported to be related to the pH and pKa of the local anesthetic solution (3). Increasing the pH of the solution decreases the H ion concentration. Theoretically, if the H ion causes the skin wheal pain, discomfort should be lessened if the pH is increased (bicarbonate added). The fraction of nonionized local anesthetic is increased with alkalinization. This may result in more rapid inhibition of nociceptive receptors. An alternate theory centers on the decreased sensitivity of nociceptive receptors to the nonionized form of local anesthetic (3).

Procaine (pH 4.3) is more acidic but less painful than lidocaine (pH 6.3) (5). On the other hand, 2-chloroprocaine (pH 3.0) is no more painful than lidocaine (3). These observations, in conjunction with our study, would seem to refute any consistent relationship between the pH of the local anesthetic solution and the pain of a skin wheal.

We attempted to minimize concern about the efficiency of our intradermal anesthetic for a subcutaneous blood vessel by placing the wheal directly over the vessel. Entry into the blood vessel occurred immediately after catheter passage through the skin wheal.

The slight but statistically significant increase in pain score between a 20- and 16-gauge intravenous catheter insertion after intradermal anesthesia is of questionable clinical relevance. If intradermal anesthesia is used, a large-bore intravenous catheter can be inserted for its clinical advantages with only a minimal increase in patient discomfort.

In summary, we have shown that the addition of sodium bicarbonate to commercially prepared lidocaine does not decrease the pain associated with an intradermal skin wheal. After intradermal anesthesia, there is a slight but statistically significant greater pain with insertion of a 16-gauge intravenous catheter as compared with a 20-gauge catheter.

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Airway Management for Trauma Patients With Potential Cervical Spine Injuries

Randolph H. Hastings, MD, PhD, and James D. Marks, MD

Department of Anesthesia, San Francisco General Hospital, University of California, San Francisco, California

Anesthesiologists are often involved in the initial resuscitation and management of trauma victims with possible cervical spine injuries. They should recognize the situations in which such injuries are likely, be familiar with evaluation of the cervical spine, and understand the risks and benefits of alternative approaches to airway management. Crosby and Lui (1) recently published for the anesthesiologist an excellent review of the anatomy, biomechanics, and disease processes affecting the cervical spine. In this article, we review the mechanisms of traumatic cervical spine injury, physical and radiologic examination, and methods for initially stabilizing the injured spine, and we focus on airway management and tracheal intubation techniques. There are no guidelines for choice of tracheal intubation technique based on the clinical situation. Different authors recommend awake tracheal intubation (2-6), direct laryngoscopy with head and neck stabilization (3,7,8), or cricothyroidotomy (3,4,9,10), but none consider whether a particular technique may be either appropriate or contraindicated in some circumstances. Crosby and Lui suggest that the method is generally unimportant as long as a cervical spine injury is recognized and reasonable care is taken with tracheal intubation. However, the risks and benefits of various approaches may vary according to the circumstances of specific cases. We review the advantages and disadvantages of alternative methods of establishing an airway in patients with actual or potential cervical spine trauma and propose that anesthesiologists develop a case-specific strategy for airway management.

Mechanism of Injury

The cervical spine (C-spine) is the most mobile portion of the vertebral column and the least supported.

Thus, it is the most susceptible to excessive movement and injury during impact accidents. The potential types of injury include hyperextension, hyperflexion, compression, rotation, and penetrating injuries. Hyperextension injuries are common in falls and can occur with blows to the face or head, whereas hyperflexion may result from acute deceleration in motor vehicle accidents (11). Instability may result when all the anterior support elements (the anterior and posterior longitudinal ligaments, the vertebral bodies and disks) or all the posterior elements (the capsular ligament, facet joints, interspinous and intraspinal ligaments) are disrupted (12). The likelihood of instability increases in more forceful accidents and when there is both rotation and linear displacement of the spine (13). In an unstable spine, normal movement and loads can disrupt anatomic relationships, causing pain or neurologic defects (14). Between 25% and 75% of all traumatic C-spine injuries are unstable (15-19). After hyperextension the C-spine is more stable in flexion. The reverse is true for hyperflexion injuries (12).

Evaluation

History

Cervical spine injuries occur in 1.5%-3% of all major trauma cases (15,19-22). The types of accidents include motor vehicle accidents, falls, diving accidents, blunt head and neck traumas, penetrating neck injuries, and contact sports injuries. Motor vehicle accidents cause 50%-70% of C-spine injuries. Most victims are men between 15 and 35 yr old (23). Daffner et al. (24) found that 10% of the drivers and 6% of the passengers in front-end collisions at speeds greater than 35 mph suffered C-spine injuries. The incidence is 6%-10% in head-first falls (25,26) and 3% or less for other accidents (lower speed motor vehicle accidents, blunt head trauma, or side- or foot-first falls (15,19, 21-23,26-29). The incidence of C-spine injuries in head trauma victims is 1%-3% in adults and 0.5% in

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Address correspondence to Dr. Hastings, San Francisco General Hospital, Department of Anesthesia, 35-50, 1001 Potrero Avenue, San Francisco, CA 94110.

Table 1. Frequency of Cervical-Spine Injuries in Pediatric Trauma

Study	Number of patients	C-spine injury		Age range
		No.	%	
Rachetky (30)	2133	25	1.2	2-17 yr
Lally (31)	187	1	0.5	1 mo-18 yr
Roshkow (32) ^a	45	0	0	1-12 yr

^aHead-first falls.

children, no higher than the figures for trauma victims in general (15,21,27-30).

Young children are less vulnerable to C-spine injury (Table 1), presumably because they weigh less and have more cartilage than adults (30-32). The vulnerability increases with the age of the child (30,33), and the risk is greater in more violent accidents. Bohn and colleagues (34) found high C-spine injuries in 14 pediatric high-velocity motor vehicle accident victims (aged 2-14 yr) with multiple trauma and severe head injury. Cervical spine injuries in children less than 2 yr old are almost exclusively at C-1 or C-2 because the facet joints at these levels are more horizontal and the ligaments are more lax than in adults (35).

Physical Examination

Table 2 shows the key association between C-spine injury and neck pain or tenderness in alert trauma patients (15,21,22,26,28-31,36). There are several case reports of unrecognized C-spine injuries (37-39), but these patients had either slight neck discomfort or altered mental status (20,26,29,36). Alert patients without neck pain or tenderness should not have cervical injury and should not require further C-spine evaluation, neck immobilization, or special precautions during airway management. The criteria must be applied stringently, however. If a patient has the slightest amount of neck discomfort, is not fully alert, or has other very painful injuries, C-spine precautions must be maintained until the absence of injury is demonstrated.

Vertebral injury can occur without cord damage because the spinal canal is widest in the cervical region. Neurologic deficits are present in 30%-70% of patients with significant spinal column injury (23,40-43). Deficits are more frequent in patients with fracture-dislocations or with bone injuries from C-5 to C-7 (42). They range from mild sensory loss to one of several neurologic syndromes (Table 3) (11).

Two-thirds of all trauma patients have multiple injuries that may interfere with full C-spine evalua-

tion (44). These include pneumothorax, hemothorax, cardiac tamponade, blunt abdominal trauma, and major fractures of the pelvis or extremities. Facial soft tissue injuries, chin lacerations, and facial fractures are common in patients with C-spine trauma and may complicate airway management (45-47). The presence of facial injuries does not increase the likelihood of a C-spine injury above the 1%-3% incidence for trauma patients, however (48-51). Hypovolemia may be caused by bleeding from fractures or by intraabdominal hemorrhage. The patient may also have cardiovascular or respiratory compromise because of spinal cord injury (52). Spinal shock is the syndrome of hypotension, bradycardia, areflexia, and gastrointestinal atony lasting days to weeks after cord injury. Loss of vasomotor tone with injuries above T-7 can cause hypotension, and more cephalad lesions result in greater cardiovascular effects. Bradycardia results from unopposed vagal tone after losing the sympathetic stimulation through the T-4 to T-5 cardiac accelerator fibers.

The degree of respiratory compromise depends on the level of the lesion. Patients with injuries at or above C-4 suffer respiratory failure because of lack of diaphragmatic function. Patients with lower lesions may have up to 70% reduction in forced expiratory volume and in forced vital capacity from the loss of intercostal muscle tone and activity and may also have reduced vital capacities because the loss of abdominal muscle tone flattens the hemidiaphragm, preventing it from developing maximal tension (53). Patients with cervical cord injuries are at risk of respiratory failure because of decreased ability to cough and clear secretions, immobility, and abdominal distention.

Radiologic Examination

The three standard plain views of the C-spine (the cross-table lateral, anterior-posterior, and open-mouth views) should be obtained early in the evaluation. All seven vertebrae must be examined because 20% of all C-spine injuries are at C-7 (54,55). Pulling the arms and shoulders caudad may be necessary to see C-7. If this is insufficient, raising the arm closest to the film over the head and depressing the opposite arm (the swimmer's view) may expose it. Additional views, such as obliques, flexion-extension views, or pillar views may clarify suspicious areas on the standard views. The "gold standard" is computed tomography (CT) scan. It is superior to plain films in identifying injuries at C-1 or C-2, showing fine detail and resolving tissue densities (56). Fractures in an axial plane are difficult to identify by CT scan and ligamentous injuries may not be appreciated, however (57). Magnetic resonance imaging scan may

Table 2. Cervical-Spine Injury and Neck Pain or Tenderness in Alert Trauma Patients

Study	No. of patients		Study	No. of patients	
	With C-spine injury	With neck pain		Without neck pain	With C-spine injury
Fisher (29)	5	5	Fisher	328	0
Roberge (26)	6	6	Roberge	141	0
Bayless (21)	2	2	Bayless	122	0
Bachulis (15)	65	65	Neifeld (28)	145	0
Ringenberg (36)	253	247 ^a	Kreipke (22)	324	0
Lally (31) ^b	16	16			
Rachesky (30) ^b	21	21			

^aSix patients with other painful injuries did not report neck pain.^bPediatric trauma.**Table 3.** Neurologic Syndromes Possible With Cervical-Spine Injury

Syndrome	Findings
Brown-Sequard	Ipsilateral paralysis Ipsilateral position and vibration sense loss Contralateral temperature and pain sense loss
Acute central cord	Bilateral motor loss, arms>legs Bladder control loss Variable sensory loss
Anterior cord	Bilateral motor, pain, and temperature loss Preserved position and vibration sense

improve recognition of spinal cord pathology. However, routine C-spine CT or magnetic resonance imaging scanning of every trauma patient would be impractical because of the time and the risk associated with transporting a potentially unstable patient to the scanner.

A radiologist should evaluate emergency C-spine films, but the anesthesiologist should have the skill in reading them also, as the condition of the spine will affect the choice of airway management technique. Evaluation includes the alignment of the vertebrae, the condition of the bones and cartilage, and the width of the soft tissue spaces and intervertebral spaces (the ABCs of cervical radiograph interpretation—Alignment, Bones, Cartilage and soft tissue spaces) (58). Alignment is best assessed by tracing four anatomic lines on the cross-table lateral view (Figures 1 and 2A). Spinous processes, vertebral bodies, and transverse processes should be aligned from one level to the next on the anterior-posterior view. Misalignment may be gross (Figure 3) or subtle (Figures 4 and 5). Fractures should be sought on all views by tracing the cortex around the vertebral bodies, lamina, pedicles, spinous processes, and dens (Figure 6). Compression fractures appear as wedging and increased density of the anterior part of the vertebral body or loss of more than 3 mm body height anteriorly. On the open-mouth view, the gap

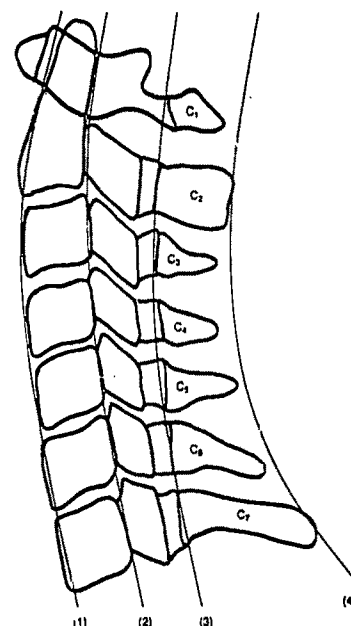


Figure 1. Diagram of the lateral view of the cervical spine demonstrating normal alignment. Lines drawn through the anterior margins of the vertebral border (1), the posterior margins (2), the junction between the lamina and spinous processes (3), and the tips of the spinous processes (4) should be smooth curves. Lines (2) and (3) are the approximate boundaries of the spinal canal. (Reprinted with permission of the publisher. From Williams C, Bernstein T, Jelenko C. *Essentiality of the lateral cervical spine radiograph*. Ann Emerg Med 1981;10:198-204.)

between the lateral masses of C-1 and the dens should be equal on the right and the left sides, and the lateral masses should not extend beyond the body of C-2 (Figure 2C). Deviation indicates a fracture of the vertebral arch of C-1, a Jefferson fracture (Figure 7) (59). Assessment of cartilage includes the disk spaces and facet joints. The disk spaces should be uniform and of roughly equal height and width at all levels. The facet joints, the articulations between the lamina and pedicles of adjacent vertebrae, should be roughly the same width at all levels. The pillar view, angled 35° toward the feet and centered on the

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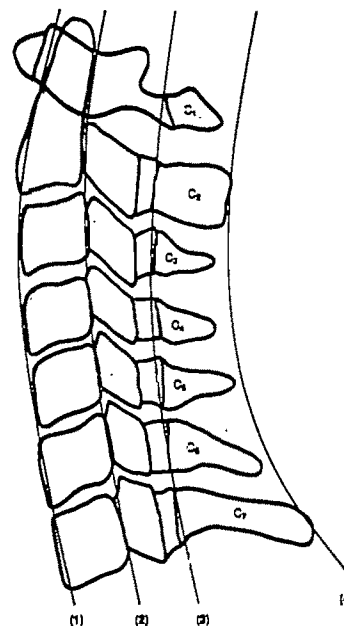


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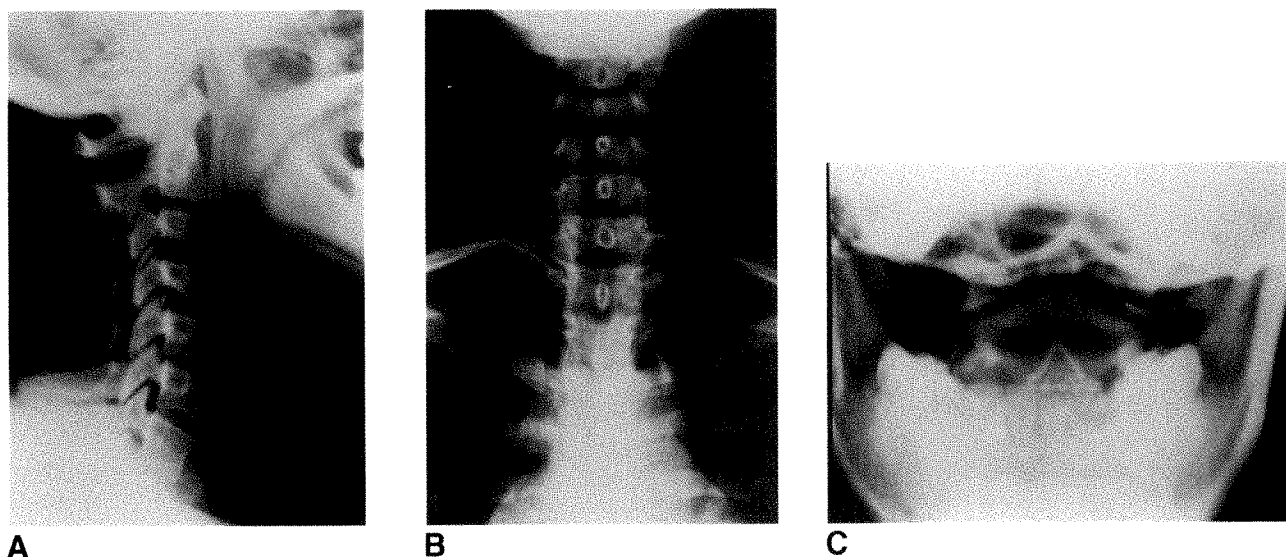


Figure 2. Standard roentgenographic views of a normal cervical spine. (A) Cross-table lateral, (B) anterior-posterior, (C) open-mouth.

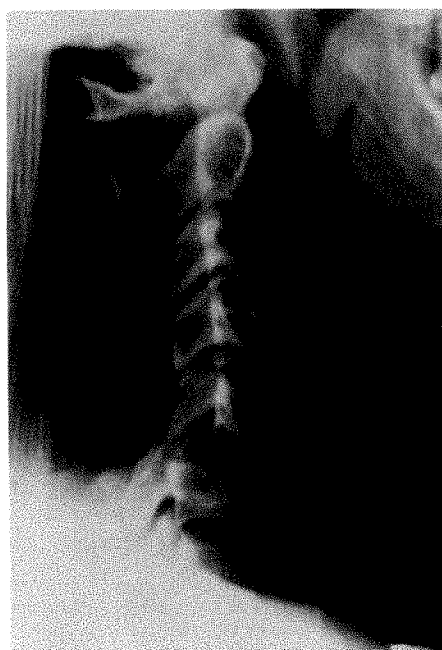


Figure 3. Lateral C-spine roentgenogram of a 27-yr-old man who fell off a cliff, showing anterior subluxation of C-5 on C-6 with bilateral locked facets. Compare with the diagram in Figure 1 and the normal radiograph in Figure 2A.

suprasternal notch, may be used to examine the facet joints and the vertebral arches. Widening of the soft tissue spaces suggests hemorrhage, edema, abscess, foreign body, or tumor, and may be the only sign of an injury at C-1 or C-2 (Figure 8). It should also alert the anesthesiologist that airway structures may be distorted and tracheal intubation could be difficult.

Table 4 summarizes the studies of the sensitivity of

roentgenography in diagnosing C-spine injuries (15-17,55,60,61). The cross-table lateral view missed 15%-20% of C-spine injuries, and the combination of the cross-table lateral view, anterior-posterior, and open-mouth views missed 8% of fractures. The missed injuries were often unstable. As the sensitivity of plain radiographs is only 75%-90%, negative plain radiographs cannot be used as sufficient criteria for ruling out a C-spine fracture, especially if a patient is at high risk. For example, a victim of a head-first fall has a 10% chance of having a C-spine injury. Given a 10% false-negative rate, a set of roentgenograms negative for spine injuries reduces the probability of an injury to 1%, not to 0. Roentgenograms suggestive of injuries should be regarded as positive, unless further studies resolve the uncertainty.

Signs of instability on the regular roentgenograms include subluxation of greater than 3.5 mm, traumatic disk space widening or narrowing, and kyphosis (rotation of adjacent vertebrae relative to each other in a sagittal plane) of greater than 11°. Tear-drop fractures, bilateral facet dislocations, hangman's fractures, and hyperextension fracture dislocations are potentially unstable injuries (13). However, C-spine stability may be difficult to determine from the standard plain radiographs; and special studies, such as controlled flexion-extension roentgenography, are sometimes required (Figure 4). The safest approach in emergency situations may be to treat all injuries as unstable.

Summary

Table 5 divides trauma patients into risk groups for C-spine injury based on history, physical examination, and roentgenographic findings. Victims of head-first

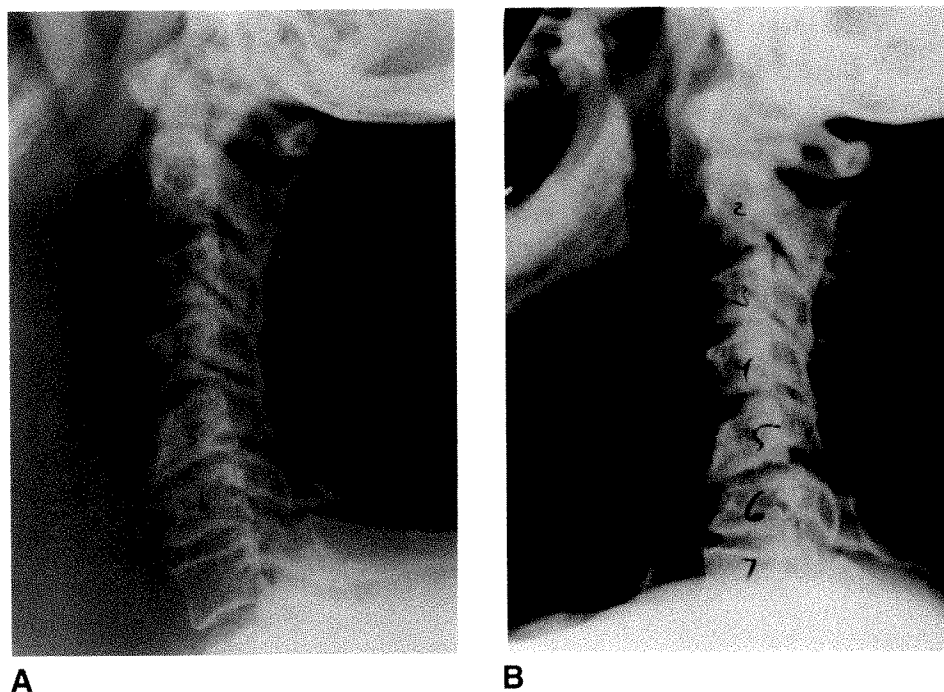


Figure 4. Lateral C-spine roentgenograms of a 63-yr-old man after a motor vehicle accident. The initial roentgenogram (A) shows only degenerative joint disease. A subsequent roentgenogram (B) taken with neck flexion 2 days later shows anterior subluxation at C5-6. The posterior alignment of the vertebral bodies and the spinolaminar line are disrupted at C-6.

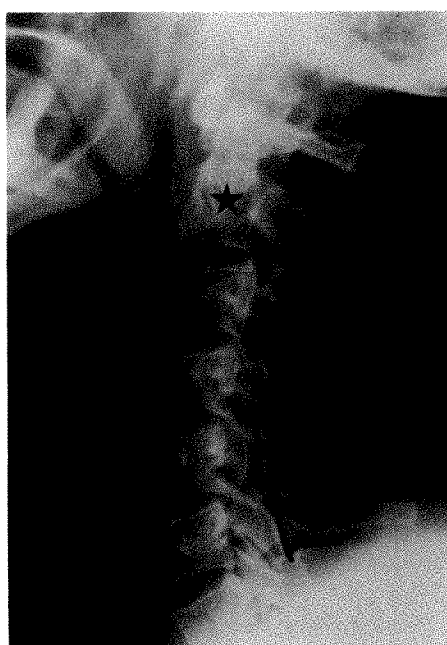


Figure 5. Hangman's fracture in a man who fell downstairs. Note the subtle misalignment of the vertebral body at C-2 (★) and the interruption of the spinolaminar line.



Figure 6. Hyperextension injury with a tear-drop fracture at C-4 (arrow). These are often unstable injuries. The fracture results from avulsion of a ligament insertion and only occurs with a forceful accident.

falls and high-speed motor vehicle accidents are at high risk (approximately a 10% chance of C-spine fracture). All other trauma patients are in the low-risk group with a 1%-3% incidence of C-spine injury. The diagnosis of

C-spine fracture is made by roentgenography or CT scan, or is presumed because of neurologic deficit. Alert patients without neck pain or tenderness, patients with

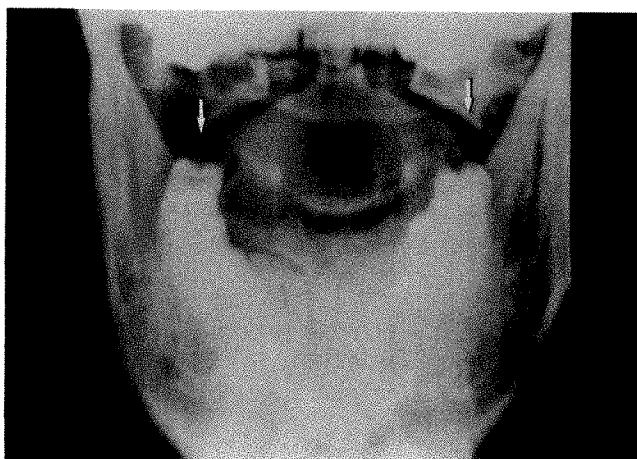


Figure 7. Jefferson fracture seen on open-mouth view. Arrows point to the lateral masses of C-1, extending lateral to the body of C-2.

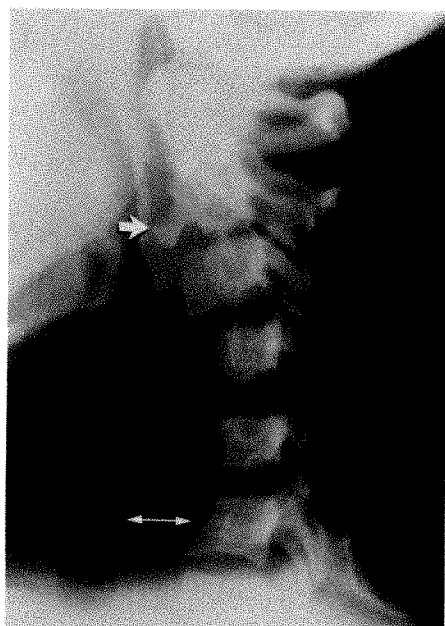


Figure 8. Avulsion of the anterior margin of C-2 (large arrow) accompanied by significant soft tissue swelling, delineated by smaller arrows. The space between the anterior border of C-2 and the pharyngeal air density should be no wider than 7 mm. The space between the air density and the body of C-7 should be no greater than 2 cm. This is the rule of 27: 2-cm maximum width at C-7 and maximum width at C-2 of 7 mm.

normal C-spine CT scans, and low-risk patients with a full set of normal C-spine roentgenograms are presumed to have normal C-spines. A high-risk patient with plain film radiographs showing normal C-spine still has a 1% or greater chance of having a C-spine injury because plain radiographs are not 100% sensitive.

Table 4. Sensitivity of Cervical-Spine Films

Study	View	Number of patients with C-spine injury	Sensitivity ^a (%)
Streitwieser (55)	CTL	44	82
	3 Views	38	92
Shaffer (16)	CTL	35	74
Bachulis (15)	CTL	90	77
Ross (17)	CTL	13	85
	3 Views	13	92
MacDonald (60)	CTL	92	92
Freemyer (61)	3 Views	33	91

CTL, cross-table lateral view.

The three views: cross-table lateral, anterior-posterior, and open-mouth.

^aSensitivity = $100 \times \text{true-positives} / (\text{true-positives} + \text{false-negatives})$.

Airway Management

The trauma patient's neck must be immobilized as soon as help arrives at the scene of an accident until complete evaluation shows there is no injury. Soft collars are unsatisfactory for this purpose because they permit 75% of normal neck movement (62). Rigid collars, such as the Philadelphia and the extrication collars, reduce flexion and extension to about 30% normal and rotation and lateral movement to about 50% (63). The best immobilization method is to secure the patient to a hard board from the head to buttocks or feet, place sandbags at either side of the head and put a rigid collar around the neck. This decreases movement to roughly 5% of normal (64). Cervical traction in the field is not recommended because the amount or direction of the force cannot be judged accurately and is likely to change during transport (11).

Anesthesiologists are concerned about what manipulations of the head and neck are safe if the C-spine is unstable, how much movement is permitted, and what might be done to protect the spine during tracheal intubation. Unfortunately, there are few studies to guide airway management in these situations and these do not provide definitive guidelines. Consequently, airway management plans must depend on the anesthesiologist's judgment of what may be safe. In this section, we discuss the advantages, disadvantages, and potential risks of several airway interventions for patients with possible C-spine injury. We also discuss the development of a case-specific airway management plan for patients with potential C-spine injuries based on the limited studies, the estimated risks of iatrogenic spinal cord injury, and the anticipated benefits and pitfalls of the various airway control techniques in specific clinical situations.

Techniques

Airway support. Airway obstruction is relieved by chin lift, jaw thrust, continuous positive airway pres-

Table 5. Risk of Cervical-Spine Injury

Known injury	High-risk group (>10%)	Moderate-risk group (1%-2%)	No-risk group
Positive C-spine roentgenogram or CT scan	Front-end MVA > 35 mph without seatbelt	MVA	Alert patient without neck pain or tenderness
Neurologic deficit	Head-first fall	Head injury	Negative C-spine roentgenograms (3 views)
	Equivocal C-spine roentgenograms	Non-head-first fall	Negative C-spine CT scan
		Contact sport injury	
		High-risk group with C-spine roentgenograms negative for injuries	

CT, computed tomography; MVA, motor vehicle accident.

sure, or nasal or oral airway insertion. Chin lift and jaw thrust might move the neck and could damage an unstable spine. Aprahamian et al. (65) reported that both maneuvers caused a greater than 5-mm widening of the disk space in a fresh cadaver with C5-6 instability. A rigid collar did not reduce the amount of displacement. Oral or nasopharyngeal airway insertion caused minimal movement. Thus, chin lift and jaw thrust might be risky if the C-spine is unstable, but there was only one subject in this study and the mobility of the cadaver's neck may have been less than that of a living patient. There are no outcome studies demonstrating that the maneuvers are dangerous in patients. Long-term airway control is not secure with bag and mask ventilation, and other procedures are needed to secure the airway.

Direct laryngoscopy. Direct laryngoscopy is the fastest and surest method of intubating the trachea. The airway is securely controlled without surgical intervention. Combative patients can be anesthetized and paralyzed for the procedure. However, some authors fear that neck movement during direct laryngoscopy may injure an unstable spine (2-6,9,10). Atlanto-occipital extension is essential to bring the larynx within line-of-sight of the mouth (66) and expose the vocal cords (67,68). Horton et al. (69) showed that there was also significant atlanto-axial extension but minimal movement in the lower C-spine during direct laryngoscopy in anesthetized volunteers. Thus, patients with unstable C-1 or C-2 injuries might be most vulnerable to neurologic damage from atlanto-occipital extension.

Two studies have demonstrated that direct laryngoscopy disturbs the C-spine in anesthetized volunteers (70) or in cadavers with unstable spines (18). In both studies, neck movement was not prevented by stabilization attempts. In-line traction on the head and neck reduced atlanto-occipital extension and flexion in the lower C-spine by 60%. In the cadaver study, axial traction stretched the spinal cord, a potentially harmful effect (18). Sudden worsening of neurologic deficits has been reported when traction is applied for spine stabilization (71) or to expose C-7 on

radiographs (72). There are no studies showing that traction protects the spine during laryngoscopy.

Neck movement can clearly result in neurologic injury. New neurologic deficits are 7.5 times more frequent if a C-spine injury is unrecognized (73), and up to 10% of patients with C-spine injuries will suffer neurologic deterioration if immobilization is not implemented (23).

Is neck movement during direct laryngoscopy associated with neurologic risk? Four studies of neurologic outcome after direct laryngoscopy with head and neck stabilization found no evidence of neurologic deterioration after intubation in 62 patients (8,74-76). Thus, direct laryngoscopy does not cause frequent injury in C-spine-injured patients. However, these studies are retrospective, and 62 patients are too few to conclude that there is negligible risk. If the results of the four studies are pooled, the 95% confidence limits for risk of neurologic deterioration with direct laryngoscopy would be 0%-7% (77). A study with no change in neurologic outcome in 475 patients would be needed to show the risk was less than 1% (77). In the best-described of these studies, Rhee et al. (76) found that 6 of 18 patients had stable injuries and only 7 had C-1 or C-2 injuries; the injuries, we believe, put the patient at greater risk. Finally, although an adverse effect of direct laryngoscopy has not been demonstrated in the published studies, there is anecdotal evidence for catastrophic results from direct laryngoscopy without head and neck stabilization. For example, we know of two cases of quadriplegia or death after laryngoscopy in patients with unrecognized C-spine injuries (unreported data).

Difficult or failed tracheal intubation may be another danger of direct laryngoscopy in patients with potential C-spine injury. Head and neck stabilization prevents complete alignment of the mouth and glottis, and the person stabilizing the head and neck is in the way of the laryngoscopist. Blood in the pharynx, facial and pharyngeal edema, facial fractures, and soft tissue injuries are common in patients with C-spine injuries (48,49) and may interfere with laryngoscopy. Finally, C-spine fractures can cause he-

matoma and edema formation around the larynx. Prevertebral swelling associated with C-spine injuries caused airway compromise in three patients reported. Laryngeal anatomy was distorted, resulting in difficult direct laryngoscopy in two patients and necessitating fiberoptic laryngoscopy in the third (78-80).

Cricothyroidotomy. Cricothyroidotomy is a rapid but invasive method of controlling the airway. It might be executed without moving the neck, but there are no studies proving this. Cervical spine immobilization may make the operation more difficult. There are no studies of neurologic outcome after cricothyroidotomy in patients with C-spine injuries.

McGill et al. (9) described the experience with 38 emergency cricothyroidotomies performed by surgical and emergency medicine residents. The 14 immediate complications (32%)—execution time greater than 3 min, inability to place the tracheal cannula, minor bleeding, and placement of the cannula into the trachea at a site other than the cricothyroid membrane—were ascribed to the resident's inexperience and none were fatal. Spaite and Joseph (81) reported 16 emergency cricothyroidotomies performed outside the hospital by emergency medical personnel. The procedure failed to secure the airway four times (25%). All 16 patients had severe injuries, most were in cardiac arrest when intubated, and only three survived. The authors concluded that the use of cricothyroidotomy in severely injured patients, possibly beyond recovery, makes it impossible to determine if the procedure would be safe and would improve outcome in salvageable patients.

Transtacheal ventilation. Transtacheal ventilation can bypass the need for cricothyroidotomy or direct laryngoscopy until the stability of the C-spine is determined or the trachea is intubated using another method, such as fiberoptic laryngoscopy. It is an effective mode of oxygenation and ventilation (82), but it does not protect against aspiration and it may not allow adequate hyperventilation for patients with increased intracranial pressure. Moreover, the equipment must be collected in advance and must be adaptable for patient transport. It may be difficult to perform if the head cannot be extended. The significant complications are barotrauma and catheter dislodgement. Smith et al. (83) reported eight nonfatal complications in 28 patients (29%) with emergency transtacheal ventilation: mediastinal and subcutaneous emphysema, 3 patients; exhalation difficulty, 4; and arterial perforation, 1.

Awake tracheal intubation. Awake tracheal intubation reliably secures the airway but may not be

appropriate if rapid intubation is necessary. Several authors have recommended awake techniques for patients with potential C-spine injuries, believing this will avoid moving or endangering the spine (2-6). Although the techniques do not depend on atlanto-occipital extension as direct laryngoscopy does, there is no documentation that they minimize neck movement. Aprahamian et al. (65) observed 5-mm posterior subluxation with blind nasotracheal intubation in the cadaver with C5-6 instability, but they believed this was due to hand pressure on the neck and not from insertion of the endotracheal tube.

Neurologic outcome with awake tracheal intubation compares favorably to outcome with direct laryngoscopy. Meschino and coworkers (84) retrospectively compared 233 patients with C-spine injuries who were not intubated with 136 C-spine-injured patients who received awake tracheal intubation. Although the injury severity score was higher in the intubation group, the percentage of patients with worsened neurologic status between initial examination and discharge was the same in the two groups. They do not report what techniques were used, how many injuries were unstable, or what the distribution of injuries among different levels was. Again, it is not clear in a retrospective study how thorough the preintubation neurologic examination was. However, the size of the study would be sufficient to place the risk of neurologic deterioration due to awake tracheal intubation at less than 4% with 95% confidence (77).

The fiberoptic technique allows intubation under direct vision and has a success rate close to 100% in skilled hands (85). It may be rendered more difficult by salivation or pharyngeal bleeding secondary to previous attempts at retrograde or blind nasal techniques. Successful fiberoptic tracheal intubation requires a cooperative patient, a secretion- and blood-free airway, pharyngeal space unrestricted by edema or tumor, and adequate topical supraglottic and infraglottic anesthesia. Coughing or bucking will result in failure and might threaten an unstable spine, but anesthetizing the larynx and pharynx might increase the possibility of aspiration. However, Ovassapian et al. (86) found no evidence of aspiration by history, physical examination, or chest roentgenography in the first 24 h after fiberoptic intubation with laryngeal anesthesia in 105 patients at risk for aspiration. Fiberoptic intubation may be more difficult in patients with head and neck immobilized on a rigid board because they cannot sit. In the supine position, the tongue and pharyngeal tissues may fall into the posterior pharynx, obscuring the space for endoscopy. Secretions and topical anesthetics are also more likely to pool in the throat and may gag the patient.

Retrograde tracheal intubation over a wire passed through the cricothyroid membrane and out the nose

or mouth is rapid and has a high success rate in the trauma patient (87). Blind nasotracheal intubation is successful in more than 90% of patients but requires multiple attempts in 67%–90% of patients (88–90). Thus, it may be slower and cause trauma to the nose or pharynx. It is contraindicated in patients with midface or basilar skull fractures because of the risk of entering the cranial cavity (91).

Summary. Direct laryngoscopy is the fastest non-invasive method of securing the airway but requires atlanto-occipital extension. Head and neck stabilization reduces, but does not prevent, spine movement during direct laryngoscopy. Its effect on outcome has not been studied. Head and neck stabilization may make tracheal intubation more difficult with any technique. There is no evidence that any of the techniques are either safe or dangerous in patients with unstable C-spines. Three small studies of emergency cricothyroidotomy and transtracheal ventilation report a 25%–30% complication rate but no fatalities. These techniques have not been studied specifically for C-spine trauma.

Management Plan

Many airway management plans would be reasonable for patients with potential C-spine injuries because there is no evidence for the superiority of any individual tracheal intubation technique. Rhee et al. (76) and Crosby and Liu (1) recommend that anesthesiologists choose the technique with which they have the most expertise. However, the studies of neurologic risk with tracheal intubation are too small to establish that the direct laryngoscopy and awake techniques are equally safe in all situations. Certainly, a technique with a 0.1% risk of neurologic deterioration or death would be preferable to one with a 4% risk. We suggest that anesthesiologists exercise professional judgment about the safety and appropriateness of the various methods on a case-specific basis.

The urgency of airway intervention is the most important factor in planning airway management for patients with potential C-spine injuries. Other considerations include the assessment of the risk of cord injury with head and neck movement, the airway anatomy, the patient's degree of cooperation, and the anesthetist's expertise. The following sections discuss development of case-specific strategies for airway management of patients with C-spine trauma.

Immediate intervention. Patients may need immediate airway control because of hemodynamic instability, respiratory failure, high aspiration risk, or elevated intracranial pressure. They should initially receive oxygen by bag and mask with assisted venti-

lation. Airway obstruction may be relieved by continuous positive airway pressure (a "tight bag"), oral or nasal airway insertion, chin lift, or jaw thrust. The front half of the rigid collar may need to be removed for chin lift and jaw thrust. After establishing ventilation, direct laryngoscopy is the fastest and surest method of securing the airway. The neurosurgeons at our institution recommend that the head and neck be stabilized in a neutral position for direct laryngoscopy without pulling on the head. We remove the front half of the rigid collar before inducing anesthesia because it interferes with opening the mouth. Succinylcholine may be used for muscle relaxation without danger of hyperkalemia if the injury occurred within 48 h (92). We try to avoid neck flexion, and we extend the head the minimum amount necessary to see the cords. The amount of spine movement is the same with curved or straight blades (70).

Direct laryngoscopy is probably the method of choice for immediate airway control of patients with actual or potential C-spine injuries. The risk of neurologic complications from direct laryngoscopy in patients with unstable C-spines has not been quantified, although there is evidence that significant complications can result from cricothyroidotomy or transtracheal ventilation (9,81,83). Cricothyroidotomy or transtracheal ventilation may be indicated in patients with anatomic features that portend difficult direct laryngoscopy under normal circumstances, because direct laryngoscopy will be even more difficult with head and neck stabilization. As anesthesiologists cannot easily practice cricothyroidotomy and as the reported complications seem related to inexperience (81), emergency cricothyroidotomy is best performed by an experienced surgeon.

Urgent intervention. In some situations involving potential or known C-spine injury, control of the airway may be urgent but immediate intervention is unnecessary. Although the severity of other injuries may preclude a definitive workup and formal stabilization of the C-spine injury, there may be adequate time for considering other techniques for securing the airway. Awake techniques, especially fiberoptic tracheal intubation, may be considered for these situations. Although there is no proof that these methods minimize C-spine movement, they do not depend on atlanto-occipital extension and the head and neck stabilizing devices can be left in place, which is not the case with direct laryngoscopy. Furthermore, Meschino's study of neurologic outcome after awake tracheal intubation had twice as many patients with C-spine injuries as all the outcome studies after direct laryngoscopy (84), so the safety can be proclaimed with somewhat greater confidence. However, an anesthesiologist who believes direct laryngoscopy is

safe could justify its use because there is no direct evidence of greater neurologic risk compared with other techniques. Fiberoptic laryngoscopy may be technically difficult or impossible in patients with pharyngeal edema, copious secretions, or blood in the airway. Awake techniques are generally inappropriate for uncooperative patients.

Nonurgent cases. Stable trauma patients with less urgent problems, such as a victim of a motorcycle accident with a tibia/fibula fracture, should have an operation delayed until the C-spine has been examined adequately. Should an injury be detected, appropriate therapy, such as tongs and traction, should be instituted. If general anesthesia is selected for a patient in C-spine traction, any technique of tracheal intubation may be chosen, but awake intubation might be prudent because the traction will prevent optimal positioning for direct laryngoscopy.

Conclusion

The possibility of iatrogenic spinal cord injury is a difficult problem in the acute management of trauma patients. The anesthesiologist should know how to evaluate the C-spine and estimate the chances of an injury. There is an overall 1%-3% risk of C-spine injury in major trauma patients. Victims of head-first falls or high-speed motor vehicle accidents have a 10% or greater chance of an injury, and C-spine roentgenograms showing normal results do not eliminate the possibility of an injury. Special treatment is unnecessary in alert patients without neck pain or tenderness, because they are not likely to have C-spine injuries.

There are few data to guide the anesthesiologist in selecting appropriate airway management techniques. The risk of worsened neurologic deficit after direct laryngoscopy, with or without spine stabilization, cannot be estimated with certainty. Anesthesiologists working with trauma patients may use their professional judgment to establish a management plan for C-spine injury. We have described the reasoning behind our own management scheme, but many plans would be viable.

The greatest flexibility in the choice of tracheal intubation method is associated with well-developed skills in each of the potentially useful techniques. At our institution, residents practice on laryngeal models and perform awake fiberoptic laryngoscopy on all patients with mandible fractures and limited mouth mobility admitted for operation. Other indications for fiberoptic intubation in elective surgical patients include reduced range of neck motion and poor dentition. Workshops to develop the skills for fiberoptic laryngoscopy are offered at many meetings. If the

anesthesiologist does not have expertise in different tracheal intubation techniques, airway management may be directed by the anesthesiologist's skills, rather than by case-specific needs.

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Perioperative Management for Laryngotracheal Reconstruction

Richard W. Rowe, MD, James Betts, MD, and Edward Free, MD

Departments of Anesthesiology and Surgery, Children's Hospital Medical Center, Oakland, California

Pediatric patients with significant tracheal stenosis traditionally have had cricoid split operations, laser excisions, or stenting procedures (1-3). However, because of the high incidence of restenosis, a more extensive operation has been devised to resect and open the area of tracheal stenosis. The trachea is opened vertically and rib cartilage grafts are inserted to expand the circumference of the trachea (4,5). This is a report of the anesthetic management of 10 pediatric patients during their extensive tracheoplasties.

Methods

The clinical pictures of the 10 patients are summarized in Table 1.

The parents of these patients received extensive counseling from the anesthesiologist, the surgeon, and the intensivist about the nature of the operation, anesthesia, and postoperative care. The patients were taken to the operating room where standard monitors (electrocardiogram, precordial stethoscope, arterial blood pressure cuff, pulse oximeter, and temperature) were placed on them. General anesthesia was induced with oxygen, nitrous oxide, and halothane via their tracheostomy tubes. Paralysis was induced by administration of a nondepolarizing muscle relaxant, and ventilation was controlled with an FIO_2 of 1.0, while peripheral intravenous lines, radial artery lines, and, when necessary, central venous lines, were started. The pulse oximeter, ETCO_2 monitor (SARACap), and esophageal stethoscope, as well as frequent arterial blood gas analyses, were used to evaluate adequacy of ventilation.

A bronchoscopy was performed to determine the level and severity of stenosis (Table 1). The trachea was then intubated orally with an appropriately sized uncuffed endotracheal tube, or, if the trachea was

severely narrowed, an endotracheal tube was introduced through the tracheostomy site. The tip of the endotracheal tube was carefully advanced beyond the level of the tracheostomy but above the carina. The patient was prepared with sterile scrub solution from chin to umbilicus and draped. A vertical incision was made in the midline of the neck from a point superior to the level of stenosis to the tracheostomy. When adequate exposure of the trachea was obtained, a sterile endotracheal tube was passed directly into the distal trachea and the orally placed endotracheal tube was pulled back to the level of the laryngeal inlet. A sterile anesthesia breathing circuit with airway gas sampling device was connected to the endotracheal tube and the distal ends were connected to the anesthesia machine. Adequate ventilation was judged by observation of bilateral chest movement and adequacy of breath sounds from either an esophageal stethoscope or bilateral pediatric chest stethoscopes placed in the axilla, as well as by data from continuous capnography, pulse oximetry, and intermittent arterial blood gas analyses. Ventilation was easily managed, with respiratory rates of 18-30 breaths/min and tidal volumes of 15-20 mL/kg. Obstruction to ventilation occasionally occurred when the endotracheal tube was advanced to the carina. When this happened, the surgeon was requested to manipulate the endotracheal tube to the point of improved ventilation. The inspired gases were humidified throughout the procedure. Six of 10 patients required bronchodilator treatment for bronchospasm, receiving 10-20 puffs of aerosolized Alupent via their endotracheal tubes until clinical improvement was noted.

The surgical approach was made easier by having the patient's lungs ventilated by placement of the endotracheal tube directly in the distal trachea and consequently out of the area of surgical correction.

A piece of rib was harvested from the right fourth, fifth, or sixth rib on each patient. A length of up to 4 cm, depending on the length needed for repair of the tracheal stenosis, was carefully removed extrapleurally. The rib was split lengthwise and fashioned

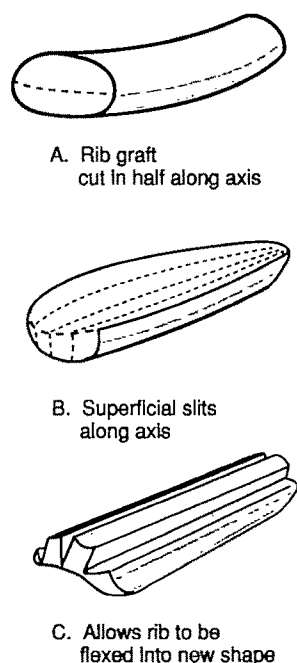
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Address correspondence to Dr. Rowe, Department of Anesthesiology, Children's Hospital, Oakland, 747 - 52nd Street, Oakland, CA 94609.

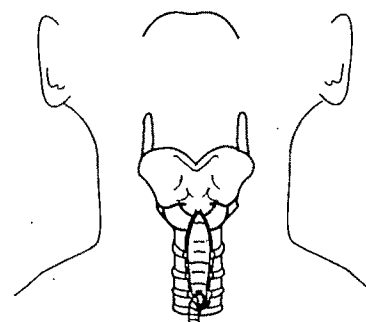
Table 1. Summary of the Patients in Whom Laryngotracheal Reconstruction Was Performed

Patient	Age at time of surgery	Tracheal obstruction (%)	Diameter of subglottis (mm)	Summary of medical problems	Preoperative medication
1	2 yr	75	<2.5	History of 28-wk GA infant with BPD, ASD repair, tracheostomy	Diuril, Aldactone, Alupent, O ₂ by tracheostomy
2	20 mo	60	<2.5	History of 29-wk GA infant with BPD, tracheostomy	Alupent
3	2 yr	75	<2.5	History of full-term infant with ASD repair, pulmonary stenosis, tracheostomy	
4	2 yr	75	<2.5	History of 26-wk GA infant with BPD, PDA ligation, tracheostomy	Terbutaline, Diuril, Aldactone, Bactrim
5	21 mo	80	<2.5	History of 28-wk GA infant with BPD, tracheostomy	Alupent
6	14 mo	90	<2.5	History of 29-wk GA infant with BPD, tracheostomy	Alupent
7	15 yr	>95	4.0	History of mental retardation and cerebral palsy, tracheostomy	
8	18 mo	50	2.5	History of 33-wk GA infant with BPD, tracheostomy	
9	4 yr	>90	<2.5	History of C1/C2 subluxation, tracheostomy	
10	4 yr	>90	<2.5	History of motor vehicle accident, tracheostomy	

GA, gestational age; BPD, bronchopulmonary dysplasia; ASD, atrial septal defect.

**Figure 1.** A summary of how the rib is transformed into a tracheal graft.

into an oval shape to fit either the posterior or anterior graft site. The rib graft was longitudinally ribbed so that it would become pliable. When it was placed over the stricture it increased the circumferential area of the grafted trachea (Figure 1). In five patients a posterior incision was made in the trachea and a graft was sutured in place with absorbable

**Figure 2.** The anterior graft was sutured in place with the perichondrial side of the graft facing the lumen of the trachea.

sutures. In all patients an anterior graft was sutured in place with the perichondrial side of the graft facing the lumen of the trachea (Figure 2). When the anterior graft was ready to be positioned, a new endotracheal tube was inserted nasally and advanced carefully into the trachea. The length of endotracheal tube needed was often longer than the standard size, and a customized endotracheal tube was fashioned by cutting the 15-mm connector at its base and using the plastic connector to join two endotracheal tubes together (6). The two endotracheal tubes were joined by careful application of methylacrylate glue to the plastic connector and by sliding the two ends of the endotracheal tube over the connector. The extra length allowed the endotracheal tube to be extended to below the site of surgical repair but above the carina. The size of the endotracheal tube was chosen by determining what size would comfortably pass through the laryngeal inlet and not cause any com-

pression against the sides of the trachea or newly placed graft. The anterior graft was sutured in place and the incision was closed.

The patients were transferred to the Pediatric Intensive Care Unit and their lungs were ventilated with a frequency of 15–20 breaths/min and peak airway pressures of 15–20 cm H₂O for 7 days. Seven patients were kept paralyzed and sedated with a constant infusion of pancuronium and fentanyl, respectively. Three patients were heavily sedated with midazolam and a continuous infusion of fentanyl after 2 days of pancuronium paralysis. The patients had neck braces fitted to prevent flexion, extension, or lateral movement of their necks. Pulmonary care, including aerosolized Alupent treatment, percussion, suctioning, and careful log-rolling of patients, was implemented to avoid atelectasis and pneumonia. All patients received prophylactic antibiotics (Cefazolin, 100 mg·kg⁻¹·day⁻¹) for 3 days. Antibiotics were continued for four patients for either a urinary tract infection or pneumonia.

Administration of pancuronium was stopped by the sixth postoperative day (POD 6), and patients were evaluated on POD 7 for possible tracheal extubation. Criteria for extubation included the following: patient was alert; had satisfactory arterial blood gas results, with F_{IO}₂ <40%, ventilatory rate <5, air leak around endotracheal tube <20 cm H₂O, and satisfactory chest radiograph. Patients meeting these criteria had their tracheas extubated and received humidified oxygen by mask. Aerosolized racemic epinephrine was used to treat stridor in four of ten patients. The tracheas of nine patients were successfully extubated by POD 10. One patient required replacement of his tracheostomy for stridor on POD 14 but was successfully decannulated in 1 mo with good result.

Discussion

Tracheal stenosis in the pediatric age group has various etiologies, including congenital and acquired lesions. All 10 patients in this series had acquired lesions. Six patients had a history of prematurity and had tracheal intubation for ventilatory management of respiratory distress syndrome. Four patients had postintubation stridor after either surgery or management of head trauma (Table 1). All patients were dependent on their tracheostomy tubes and had failed decannulation. All had severe tracheal narrowing in the subglottic region.

The choice of the surgical procedure is dependent on the degree of tracheal stenosis. Cricoid split procedures have been successful in the treatment of moderate tracheal stenosis at the level of the cricoid ring (7,8). There have been many other techniques for more severe tracheal stenosis, including surgical,

laser, and electrocautery excision of tissue (9,10). Opening of the trachea and insertion of prosthetic material, esophageal tissue, or pericardial tissue have been reported (11–13). However, the long-term results generally have been unsatisfactory because of restenosis, infection, or tracheomalacia.

The advantage of the surgical approach to the patients in this series is that these patients will have larger tracheal lumens with minimal scarring. The rib graft is an excellent implant because it becomes vascularized and remains rigid. Therefore, there is little chance of tissue rejection or weakening of the implant (14).

The anesthetic management of these patients must be tailored not only to their medical problems but also to the surgical considerations of this technique (15–18). The surgical considerations included having full exposure of the site of tracheal stenosis, as well as a still surgical field. Because many patients had a posterior graft inserted, it was desirable not to have an endotracheal tube or high-frequency jet ventilator tubing in the trachea at the time of the repair.

All six patients with a history of prematurity had bronchopulmonary dysplasia, the long-term consequence of respiratory distress syndrome. These patients were being managed with bronchodilator therapy and supplemental oxygen via their tracheostomy tubes. Respiratory management of these patients was optimally treated preoperatively to ensure that they did not have pneumonia or worsening bronchospasm. Patients with bronchopulmonary dysplasia have a higher incidence of bronchospasm, bronchial secretions, low respiratory compliance, and an increased AaO₂ gradient during their anesthetic care (19). Pediatric patients with tracheostomy tubes frequently have chronic tracheitis, which can complicate the patients' intraoperative course with airway secretions, bronchospasm, and ventilation-perfusion mismatch.

The patients in this series were given an anesthetic tailored to their respiratory problems. A combination of intravenous narcotic and inhaled anesthetics was used to obtain a deep level of anesthesia before any manipulation of the airway. Intraoperative bronchodilator therapy was also used to prophylactically treat bronchospasm.

The described anesthetic approach of placing a sterile endotracheal tube into the distal trachea has many advantages. This method was chosen over high-frequency ventilation for a number of reasons. The endotracheal tube is easily placed and secured by the surgeons. If the position of the tip were to go into the mainstem bronchi, it could quickly be detected by unequal breath sounds from the axillary stethoscopes, a rise in the inspiratory pressure of the

anesthetic circuit, a decrease in the oxygen saturation, or a change in end-tidal CO₂ or arterial blood gas analysis.

It is also possible to deliver warmed, humidified oxygen, aerosolized bronchodilator treatment, and continuous inspired halothane throughout the case via an endotracheal tube. These agents may constitute an important part of managing pediatric patients with reactive airway disease, and they cannot be delivered via a high-frequency ventilation catheter.

The main objection to high-frequency ventilation for these patients was having a catheter in the surgical field. In the pediatric airway the catheter's position must be monitored closely to ensure proper ventilation and delivery of an adequate amount of inspired oxygen, and to avoid barotrauma or movement of the surgical field (20,21). A second catheter is necessary to monitor airway pressures, and because it shares the surgical field it must be kept free of blood or secretions to function properly. A catheter for high-frequency ventilation would be in the operative field while the surgical procedure on the posterior trachea was being performed.

The postoperative course for these patients involved having their tracheas remain intubated and ventilation being controlled for seven postoperative days. After tracheal resection in adults, early tracheal extubation helps to avoid trauma to the surgical site by the indwelling endotracheal tube. However, early attempts to extubate the trachea in these pediatric laryngotracheoplasty patients resulted in movement of their grafts and stridor. Therefore, these patients were managed by continuing an infusion of pancuronium, midazolam, and fentanyl until the third postoperative day. In three patients pancuronium was discontinued while sedation was maintained. All patients were kept in neck braces to immobilize the cervical spine. Careful respiratory therapy, including aerosolized bronchodilators, chest physiotherapy, and suctioning of endotracheal tubes was continued. Since the distal end of the endotracheal tube was below the suture line in the trachea, there was little danger of traumatizing the surgical repair by suctioning from the endotracheal tube.

Nine of ten patients had their tracheas successfully extubated by the 10th postoperative day. One patient required prolonged tracheal intubation and replacement of his tracheostomy tube. Bronchoscopy revealed a granuloma at the surgical site, which was removed by laser excision. The patient was successfully decannulated 1 mo after his initial surgery.

Long-term (18 mo to 4 yr) results for all patients have been excellent. The patients have had no episodes of stridor or respiratory distress and have been undergoing speech physiotherapy with good results.

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Mainstem Bronchial Obstruction Secondary to Nasotracheal Intubation: A Case Report and Review of the Literature

Thomas E. Knuth, MD, MAJ, MC, and Jerry R. Richards, MD, MAJ, MC

Department of Surgery and Anesthesiology and Operative Services, Tripler Army Medical Center, Tripler AMC, Hawaii

Complications experienced by the trauma patient can stem from resuscitation efforts as well as from injury. In this case, a complication associated with endotracheal intubation via the nasal approach was initially attributed to the trauma. Damage to the nasal mucosa, turbinates, and the nasopharyngeal wall during nasotracheal intubation have been well described (1), but dislodgement of a nasal turbinate by a nasotracheal tube with impaction in the bronchus is an unusual complication that has not previously been reported. When signs and symptoms of bronchial obstruction are seen after tracheal intubation by the nasal approach in a trauma patient without external or radiographic evidence of chest trauma, this complication should be suspected.

Case Report

A 20-yr-old woman was an unrestrained front-seat passenger in a high-speed motor vehicle accident. She was hemodynamically stable with spontaneous respirations but was unresponsive with a Glasgow Coma Scale score of 4 on initial assessment in the emergency room. Chest radiograph and lateral C-spine radiographs were normal. Except for a fractured arm and minor facial and leg abrasions, her only apparent injury was a closed head injury. Her trachea was intubated by an emergency room physician using a Sheridan nasotracheal tube with a 6-mm inside diameter that was inserted through the left nostril. Hyperventilation was initiated, mannitol was administered, and the patient was taken for a computed tomographic scan, which revealed no cranial fractures and no intracranial mass lesions. Plans were

made for craniotomy placement of an intracranial pressure monitor and for open reduction with internal fixation of her radius fracture. Preoperative evaluation by the anesthesiologist revealed decreased breath sounds and decreased chest expansion on the left side. Suctioning of the endotracheal tube revealed no obstruction and because there appeared to be no endobronchial intubation, a chest radiograph was obtained (Figure 1). An elevated left hemidiaphragm with some left lower lobe atelectasis was seen. The endotracheal tube was in good position. Vital signs, oxygen saturation, peak inspiratory pressures, and arterial blood gas levels remained normal, so she was taken to the operating room. Anesthesia was induced with the intravenous administration of thiopental and fentanyl and maintained with isoflurane and oxygen. A left subclavian central line was inserted for central venous pressure monitoring. Shortly thereafter, the patient became difficult to ventilate with peak inspiratory pressures rising to 60 cm H₂O. Auscultation revealed decreased breath sounds on the left side without wheezing on either side. Although suctioning again failed to demonstrate tube obstruction, about 10 mL of dark blood and secretions was obtained and ventilation improved. The nasotracheal tube was replaced by a tube with a 7-mm inside diameter through the same nostril, and peak inspiratory pressures still remained elevated at 40 cm H₂O and breath sounds remained diminished on the left side. A chest tube was inserted into the left side of the chest and placed to suction, but there was no resolution of clinical findings. Rigid bronchoscopy was performed with the expectation of finding a disrupted bronchus or aspirated food or gum (dentition was intact). Instead, a 5.0- × 0.5-cm cartilaginous structure (Figure 2) consistent with a nasal turbinate was extracted from the left mainstem bronchus. Left-sided breath sounds and ventilation returned to normal and the case proceeded without further difficulty. The pathologist later confirmed that the extracted tissue was a completely intact nasal turbinate.

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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Address correspondence to Dr. Knuth, Major, Medical Corps, General Surgery Service, Tripler Army Medical Center, Tripler AMC, HI 96859-5000.

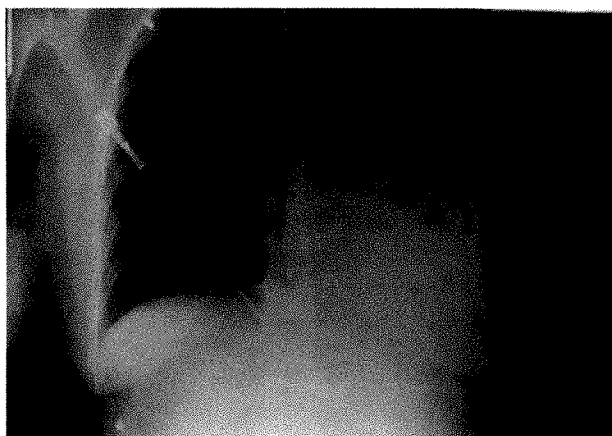


Figure 1. Emergency room chest radiograph showing slightly elevated left hemidiaphragm.

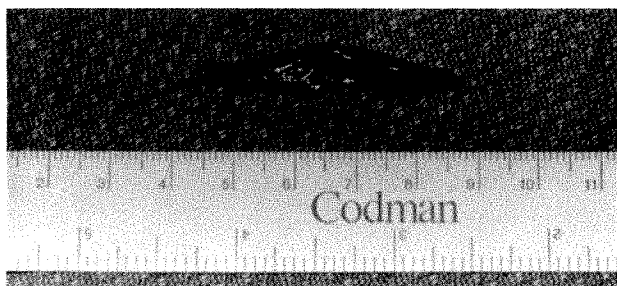


Figure 2. Bronchoscopic specimen: left nasal turbinate.

Discussion

The observation of decreased breath sounds and decreased movement of the left side of the chest led to an unsuspected finding. As the patient had no external evidence of chest trauma on physical examination and the initial emergency room chest radiograph was normal showing no rib fractures, pneumothorax, hemothorax, or pulmonary contusion, we believed that total left chest opacification on chest radiograph only a few hours later was not related to the trauma. These changes may have been related to insertion of the central line, but lack of resolution with insertion of a chest tube ruled out hemothorax, intravenous fluid infiltration, and pneumothorax. The shift of mediastinal structures on the second film raised the question of bronchial obstruction owing to aspirated food, but an aspirated nasal turbinate was not suspected.

In retrospect, nasotracheal intubation in the emergency room must have traumatized the anterior end of the inferior nasal turbinate, shearing it cleanly away from its lateral attachment to the nose. Positive pressure ventilation then gradually forced the mass into an obstructing position. Scamman and Babin (2) report a similar case with only partial avulsion of the middle turbinate secondary to nasotracheal intubation. Their case involved persistent significant nasal

bleeding, which ours did not, that led to nasopharyngeal exploration. A computed tomographic scan revealed a possible tumor, but exploration revealed a turbinate partially sheared off and hanging on a vascular pedicle. Total amputation of a turbinate as the cause of endotracheal tube obstruction has been described by Torras et al. (3) and Boysen (4), but in each case, the obstruction was remedied by simply changing the endotracheal tube or by vigorous coughing (5). Total amputation leading to bronchial obstruction has not been described.

Blanc and Tremblay (6) provide an exhaustive classification and literature review of complications associated with tracheal intubation without mentioning additional complications unique to the nasotracheal approach. Tintinalli and Claffey (1) in their list of complications specific to nasotracheal intubation include damage to the turbinates without mentioning amputation. Plugging of a nasotracheal tube by a nasal polyp (7), blood clot (8), and tumor (9) have also been described. Harvey and Amorosa (10) found that 33% of nasotracheal tubes become soiled with some type of pharyngeal tissue during intubation. The incidence of this occurrence increases to 57% when resistance is encountered during passage of the tube, 69% when bleeding is encountered, and 86% when both resistance and bleeding are encountered. Rector et al. (11), drawing from Scamman and Babin's (2) experience with turbinate avulsion, describe techniques and theory to reduce the risk of these complications. Recommendations relevant to avoiding turbinate damage are as follows: (a) Use an appropriately sized tube (5.5–6.5 mm inside diameter for women and 6.0–7.0 mm inside diameter for men depending on anatomic variation). Smaller tubes are less traumatic, but larger tubes with greater flows and ability to accommodate suctioning catheters can generally be left in place for long-term airway management. (b) Use the most patent nare (consider septal deviation, nasal lesions, and congestion owing to colds, allergies, and the human nasal cycle). (c) Use the right nostril first if all else is equal (the bevel at the tube tip will then point away from the nasal turbinates located laterally and thereby have less opportunity to snag and shear them). If the left nostril is used, the tube should be inserted upside-down and then turned once inserted past the turbinates. (d) Never force a tube (if resistance is met, retreat and try again). Also, visual inspection of the tube lumen as it passes the retropharynx and before entry through the vocal cords can help prevent obstructive complications (3,10). Kawamoto and Shimizu (12) suggest using a Foley catheter as an obstructor for the tracheal tube to prevent its obstruction, but others (3) doubt the practicality of this suggestion. Simple awareness that this complication does occur is probably the best preventative measure.

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Chronic Headache Resulting From Postoperative Supraorbital Neuralgia

David S. Klein, MD, and Raymond E. Schmidt, Jr., MD

Department of Anesthesiology, Ohio State University, Columbus, Ohio; Shenandoah Valley Pain Clinic, Staunton, Virginia; Department of Anesthesiology, National Naval Medical Center, Bethesda, Maryland

Chronic enigmatic headache is a clinical entity that can present both diagnostic and therapeutic challenges. A patient with chronic frontal headache was successfully diagnosed and treated for neuropathic pain caused by posttraumatic supraorbital nerve injury.

Case Report

A 58-yr-old woman was referred by our neurology service for evaluation of chronic right-sided frontal headache. The patient described a 30-mo history of severe, sharp pain over the right eye radiating to the right forehead. The pain occasionally radiated to the right temporal and parietal areas as well.

The pain was slightly relieved by the combination of 50 mg of butalbital, 325 mg of acetaminophen, and 40 mg of caffeine (Fioricet, Sandoz Pharmaceutical). Antiinflammatory medications provided no relief, and the pain began interrupting her usual sleep pattern. She was therefore taking 50 mg of oral nortriptyline (Pamelor, Sandoz Pharmaceutical) to facilitate sleep.

She had been repeatedly evaluated for frontal sinusitis. After skull radiographic series, a computed axial tomography scan, electroencephalography, and a magnetic resonance imaging scan, the patient was empirically treated with antibiotics. Her medical history was otherwise unremarkable. With increasing pain and lost time at work, she was referred for pain clinic evaluation.

Three weeks before the onset of her headaches, the patient underwent excisional biopsy of a "moderately sized" right frontal scalp lipoma, under isoflurane-nitrous oxide endotracheal anesthesia. After

induction of the anesthetic, 15 mL of 0.5% lidocaine containing epinephrine 1:200,000 was infiltrated locally surrounding the lesion to decrease surgical bleeding. The lesion was excised, and she recovered uneventfully from the anesthetic.

At first, her headaches were described as "mild" frontal aches that required no attention on the part of the patient. Over the course of several months, however, the headaches gradually worsened to the point where they were described as "incapacitating." The headaches were intermittent, occurring two to three times per day. The pain would begin over the right frontal area and lancinate over the vertex. The headaches lasted from a few minutes in duration to as long as several hours. On occasion, the headaches would awaken the patient from sleep. Physical examination revealed a normally developed black woman. Neurologic examination was entirely normal, but the right supraorbital notch was exquisitely tender. Percussion of the supraorbital nerve produced the constellation of complaints typical of her headaches.

Diagnostic supraorbital nerve block was performed with 0.25% bupivacaine with epinephrine 1:200,000 and 20 mg of methylprednisolone using a 27-gauge tuberculin syringe. The total volume of injectate was 0.5 mL. Moments after the injection, the pain disappeared. Palpation then revealed that the patient was no longer tender over the supraorbital notch.

The patient was given 20 mg of oral piroxicam (Feldene, Pfizer Labs) daily, and 0.5 mg of oral clonazepam and 50 mg of nortriptyline at night.

At reevaluation 2 wk later, the patient reported a dramatic decrease in the frequency of her headaches and in the severity of her pain. During the 2-wk interval after the first supraorbital nerve block, the patient reported a total of only two or three mild headaches in marked contrast to the two or three severe daily headaches before the first block. Physical examination revealed persistent tenderness over the supraorbital notch, but it was far less severe than it had been at the time of the first evaluation. The

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Address correspondence to Dr. Klein, P.O. Box 509, Staunton, VA 24401.

supraorbital nerve block was repeated using an identical technique. At follow-up 2 wk later, the patient denied any pain during the 2 wk. Several months later, the pain had yet to return. Her medications were discontinued, and the patient continued to do well.

Discussion

The supraorbital nerve is a terminal branch of the ophthalmic division of the trigeminal nerve. This cutaneous sensory nerve passes between the levator palpebrae superioris and periosteum of the roof of the orbit exiting through the supraorbital notch. It supplies sensory fibers to the ipsilateral forehead and scalp extending variably to as far as the lambdoid suture. The passage of the nerve through the supraorbital notch and the location of the nerve against the frontal bone renders it susceptible to injury.

Chronic compression of the supraorbital nerve against the frontal bone has been reported to cause "migraine" (1), and the wearing of tightly fitting swimming goggles may be the cause of chronic headaches owing to supraorbital neuralgia (2).

Although the exact mechanism of neural trauma in this case is unclear, there are several possibilities. The neuropathy could have resulted from retractor trauma at the time of surgery. Compression or stretch of the nerve could precipitate a traumatic mononeuritis, the pain developing after the inflammatory process progresses to a point where cicatrix formation around the nerve compresses the nerve at the su-

praorbital notch. This process of scar formation can be slow in onset, but a keloidlike process in this individual may have occurred.

Trauma to the nerve might have occurred as a result of the local anesthetic injection performed after the patient was induced with the general anesthetic. If the injection had been given intraneurally, a chemical neuritis might have resulted. In an awake patient, an intraneural injection is extremely painful, thereby alerting the surgeon to cease injection and to reposition the needle before damage can occur. In this case, however, the patient was anesthetized, thereby eliminating this clinical sign.

An additional possible cause is compression neuropathy secondary to anesthesia mask pressure. The nasal portion of the anesthesia mask rests directly over the supraorbital notch. As this patient's facial anatomy may have mandated increased pressure to achieve a satisfactory mask seal, the pressure of the superior border of the mask may have contributed to the trauma.

In summary, a patient with a 30-mo history of chronic headache owing to supraorbital neuralgia after excision of a scalp mass was successfully treated with two supraorbital nerve blocks that completely and permanently eliminated the pain.

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Rumination Risk of Aspiration of Gastric Contents in the Prader-Willi Syndrome

Tod B. Sloan, MD, PhD, and Celia I. Kaye, MD, PhD

Departments of Anesthesiology and Pediatrics, University of Texas Health Science Center, San Antonio, Texas

The Prader-Willi syndrome (PWS) is a rare, usually sporadic disorder characterized by infantile hypotonia, subsequent obesity with hyperphagia, and small hands and feet. Hypogonadism, diabetes mellitus, delayed psychomotor development, mental retardation, short stature, hypermobile joints, strabismus, myopia, scoliosis, kyphosis, blue almond-shaped eyes, and narrow bifrontal diameter are other features. Since its original description by Prader, Labhardt, and Willi (1), more than 200 cases have been reported. More than half of these cases have been associated with a deletion or rearrangement of chromosome 15. It has been hypothesized that lack of a critical region on chromosome 15 contributed by the father leads to the Prader-Willi phenotype (2).

During a recent anesthetic for dental rehabilitation in a child with PWS, gastric secretions were identified in the mouth during induction of anesthesia. A review of recent literature on PWS suggests that rumination (regurgitation of gastric secretions) occurs frequently in these patients and may contribute to the development of dental caries (3). We review the anesthetic implications of PWS with special reference to the unique phenotype of these patients and their increased risk of aspiration of gastric contents.

Case Report

A 17-yr-old girl was admitted for dental rehabilitation under general anesthesia. A single seizure had heralded the onset of diabetes mellitus at age 15 yr, which had been treated with diet, glyburide, and intermittent supplementation with insulin. She had typical findings of PWS with small hands with clubbing, small feet and face, and short stature (120 cm) (fifth percentile for age, average height for a 7-yr-old). She had a large protuberant abdomen and was

grossly obese (43 kg; more than 200% ideal weight for her height). She was retarded but was pleasant and cooperative despite the fact that intermittent temper tantrums, crying spells, and aggressive behavior had been reported at home and school. Pre-operative screening of pulmonary functions revealed a restrictive lung defect without obstructive components and normal results from analysis of arterial blood gases [forced vital capacity (FVC), 52% predicted; forced expiratory volume (FEV), 58% predicted, FEV/FVC, 113% predicted]. Her mother stated she had been without food or water for 10 h and informed consent was obtained for general anesthesia.

She was taken to the operating room where the usual monitors were placed. After administration of neosynephrine nasally by spray and breathing oxygen via a mask, induction of anesthesia was accomplished by intravenous thiopental, 225 mg, and ventilation via mask was easily accomplished. Intubation of the trachea was accomplished after intravenous administration of 3 mg of vecuronium with a cuffed 5.0-mm-inside diameter nasal right angle endotracheal tube. During anesthetic intubation, brownish gastric secretions were seen pooling in the posterior pharynx. Breath sounds were clear, and no secretions could be obtained by suctioning through the endotracheal tube.

Anesthetic maintenance was accomplished using isoflurane (1%–1.5% inspired) in oxygen and nitrous oxide (30%–50% inspired) with small intravenous doses of fentanyl (225 mg), and mandibular blockade, with 0.5% bupivacaine performed by the surgeons. Emergence was uneventful, and the trachea was extubated after the patient could follow verbal commands and demonstrate a head lift exceeding 5 s. Her recovery room stay was uneventful without clinical evidence of aspiration pneumonitis. Oxygen saturation fluctuated between 88% and 96%. She had an otherwise uneventful postoperative course with serum glucose of 309 mg/dL and returned home with her mother the afternoon of surgery.

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Address correspondence to Dr. Sloan, Department of Anesthesia, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284-7838.

Discussion

The clinical course of PWS is usually divided into two phases (4). The first phase, during the newborn and infancy period, is characterized by marked hypotonia, poor sucking, swallowing, coughing, crying, and episodes of asphyxia (5,6). This evolves into a second phase at age 2-5 yr, characterized by hypogonadism, mental retardation, and obesity from hyperphagia. These patients have a voracious appetite and can consume large quantities of food without satiety. The exact defect in these patients is not understood, but has been proposed to be hypothalamic dysfunction (7) or an inborn error of lipid or carbohydrate metabolism (8).

The Prader-Willi syndrome is usually sporadic, and for 20 yr after its description, the cause of the condition was unknown. In 1981 Ledbetter et al. (9) identified a deletion of the long arm of chromosome 15 (15q11-13) in some patients with PWS. When parents of these children were studied using DNA markers, the deleted chromosome 15 was usually derived from the father (10,11). In patients without a chromosomal deletion, the two different chromosomes 15 were both inherited from the mother (12). Based on these cases, the abnormalities in PWS probably result from the lack of a critical portion of chromosome 15 derived from the father.

The mechanism by which two chromosomes of the same pair can be inherited from one parent, with neither chromosome of that pair being inherited from the other parent, is unclear. One possible mechanism would be nondysjunction (failure of division of paired chromosomes) during maternal meiosis, leading to both maternal chromosomes 15 being present in the ovum. At or shortly after fertilization, loss of the paternally contributed chromosome 15 would have to occur. Whatever the mechanism, the resulting uniparental disomy leads to absence of apparently critical, paternally derived genetic material.

The concept that the parental origin of a gene influences its expression is termed genomic imprinting. This idea is contrary to the basic Mendelian principle that the parental source of genetic information does not influence the expression of the gene. The mechanism by which imprinting might occur is unclear. However, the stage at which germ-line cells are formed could represent one period during which genetic information is temporarily altered, changing it so as to permit expression in the next generation (13). Additional study of human examples of imprinting, such as PWS, will lead to a better understanding of this novel mechanism of inheritance.

The anesthetic implications of PWS have been

reviewed by Palmer and Atlee (8) in 1976 and Yamashita et al. (14) in 1983. Problems that have been identified in the perioperative period include disturbances in body temperature (hyperthermia or hypothermia), intraoperative arrhythmias (notably premature ventricular contractions), cor pulmonale, and the effects of obesity (such as reduced pulmonary reserves) (8,14-18). In addition, patients who have undergone intestinal bypass procedures must be evaluated for disturbances in fluid and electrolyte status, hepatic function, and nutritional status.

Many factors make patients with PWS prone to perioperative aspiration pneumonitis. As violent temper tantrums are associated with withholding food, and food seeking and stealing behavior are highly developed, only a well-supervised patient should be considered NPO. The physiologic set point of vomiting in PWS is abnormal, and these patients have a reduced tendency to vomit. Certainly the obese body habitus may be associated with a higher than normal incidence of hiatal hernia and increased abdominal pressure. Alexander et al. (3) surveyed the PWS Association and found that there was a 10%-17% incidence of rumination in PWS patients.

Previous reports on PWS have not discussed the potential risk of aspiration of gastric contents contributed by rumination in these patients. In animals, rumination occurs when negative intrathoracic pressure is coupled with contraction of the rumen (stomach) and esophageal antiperistalsis. In humans, voluntary contraction of the abdominal wall and/or diaphragm initiates reflux, which is allowed by spontaneous or swallow-initiated relaxation of the lower esophageal sphincter (19). This occurs most frequently in children and persists into adulthood in mentally retarded people. It is characterized by the regurgitation of food followed by rechewing, spitting, or reswallowing; there is no sign of nausea, retching, or disgust. Observation of children ruminating gives the impression that the child gains considerable satisfaction (20).

Rumination can occur in neurologically normal children (typically 3 wk to 12 mo of age); retarded individuals have an onset at an older age (21 yr). Three primary factors contribute to rumination behavior. These include organic problems that physiologically increase regurgitation (hiatal hernia, chalasias, or incompetent lower esophageal sphincter), psychodynamic factors that increase the pleasure-seeking behavior of rumination (e.g., particularly a disordered mother-infant relationship), and the development of a behavioral pattern of rumination as a learned pleasurable experience (20,21). This latter contribution may be very important in the infant who

receives little gratification from his caretakers and environment; rumination becomes a way of self-gratification and a mechanism of relieving tension (21).

A review of known cases of rumination suggests that two groups of ruminators exist (20). One group includes the psychogenic ruminators, in which rumination begins in infancy (onset 0.7–17 mo, mean 5 mo). Rumination in this first group is caused by psychodynamic factors associated with failure of maternal nurturing. A second type (labeled self-stimulating rumination) occurs almost exclusively in retarded individuals and can begin at any age from infancy through adulthood (onset 5 mo–21 yr, mean 6.8 yr) (20). Most of the latter group were males (five times the incidence in females) and functioning in the profoundly retarded category (20). It is speculated that cognitive impairment in these individuals interferes with the normal utilization of external sources of gratification. Hence, retarded individuals often seek self-directed, atypical, voluntary, pleasurable, and repetitive self-stimulating behavior (20).

In a behavioral study of a 12-yr-old institutionalized retarded ruminator, the environmental factors contributing to rumination were identified (22). The greatest incidence of rumination was in the time period after eating (2.3 times the average frequency of rumination). However, psychodynamic factors were also very important. Hence, warm, nurturing attention by a familiar caretaker reduced the incidence. Independent play and attention by individuals who did not like the child, or whom he disliked, increased the incidence. Of interest is that rumination occurred during all waking hours, including in the morning before breakfast, 14 h after dinner.

As rumination can cause diffuse destruction of dental hard tissue secondary to demineralization (decalcification) by the acidic gastric contents (23), retarded patients presenting for restoration of erosive damage may have rumination disorders. Other possible indicators of rumination are foul-smelling breath and repeated spitting or vomiting, as well as observed rumination behavior. As above, the incidence may be increased in males. Based on the literature, one would predict that removal of a ruminating child from friendly, nurturing surroundings, followed by exposure to an unfamiliar and hostile preoperative environment, may increase the incidence of rumination. Further, it appears that the customary NPO orders will not prevent this behavior.

In PWS, the reduced tendency to vomit, coupled with rumination and reduced pulmonary reserves, leads to the possibility that aspiration of stomach contents may occur with a higher than normal frequency and severity during induction of anesthesia.

Our patient was reported to be NPO for 10 h before anesthetic induction; nevertheless, gastric secretions were present in the posterior pharynx. We therefore suggest that all patients with PWS be considered at high risk for aspiration of gastric contents during general anesthesia. Efforts should be made to reduce acid secretion, increase intestinal motility, neutralize stomach contents, use body position to utilize gravity to reduce the tendency for passive regurgitation, secure the airway rapidly, decompress the stomach, and extubate the trachea cautiously. By these means, surgical morbidity and mortality related to aspiration of gastric contents in these patients may be reduced.

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Pheochromocytoma in a Patient With Eisenmenger's Complex

Timothy W. Rutter, MD, and Vildan Mullin, MD

Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor, Michigan

Pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells and is a rare (~0.1%) cause of hypertension. The tumor is found in the adrenal medulla in about 80% of cases and the treatment of choice is its surgical removal. This case is reported because of its being complicated by truncus arteriosus and Eisenmenger's complex and because a review of the literature revealed an interesting possible association between these two conditions.

Case Report

The patient was a 34-yr-old, 58-kg woman with cyanotic congenital heart disease, specifically, a truncus arteriosus type 4, ventricular septal defect, and absent intrapericardial pulmonary arteries; the pulmonary artery supply was from a right-sided branch of the aorta. The cardiac status was further complicated by the development of Eisenmenger's complex. At the age of 14 yr she underwent a right thoracotomy for an attempted repair, but because of extensive collateralization, surgery could not be performed. In May 1988, she was evaluated at an outside clinic for consideration for heart and lung transplantation but was refused. Symptoms relating to her chronic cardiac condition were those of fatigue, dyspnea when walking 50 yards, orthopnea, nocturia, and peripheral edema. The patient had a history of polycythemia and epistaxis, but no coagulation defect had been found. The patient had a hemangioma over the right mandible treated previously by radiation and was considered to have Von Hippel-Lindau's disease.

In the past year, she had experienced palpitations, flushing, diaphoresis, and central chest pain. Holter monitoring demonstrated frequent premature ventricular contractions and a 12-s run of ventricular tachycardia, as well as episodes of supraventricular

tachycardia. The patient was also noted to have poor dentition and a relative micrognathia, but evaluation in the Difficult Airway Clinic anticipated uneventful tracheal intubation. The patient was diagnosed as having a pheochromocytoma on the basis of urine analysis with elevated norepinephrine and metanephrine concentrations. Computed tomography scanning tests revealed bilateral adrenal masses. [¹³¹I]Metaiodobenzylguanidine (MIBG) scanning indicated that only the right adrenal gland contained a catecholamine-secreting tumor. The patient's laboratory workup demonstrated a hemoglobin of 17.4 g/100 mL with a hematocrit of 55.4%. Blood chemistry and coagulation studies were normal. The patient was taking 0.125 mg of oral lanoxin, 40 mg of oral furosemide twice a day, 600 mg of oral micropotassium three times a day, and 12.5 mg of oral captopril twice a day. The cardiologist was concerned that α - and β -adrenergic blockade could aggravate the right-to-left shunt; but in view of the increasing arrhythmias and chest pain, 10 mg of oral phenoxymetamine and 10 mg of propranolol were added four times a day, with a marked improvement in her symptomatology and no deleterious effects on oxygenation.

On the morning of surgery, the patient was taken to the operating room where 5-lead electrocardiogram, noninvasive blood pressure cuff, and pulse oximeter monitors were applied. Under sterile conditions and with antibiotic coverage (1 g of vancomycin, given slowly 1 h before the procedure), a central venous line and arterial line were placed. Meticulous attention was paid to the prevention of air entrainment because of the risk of paradoxical embolism. The electrocardiogram showed a normal sinus rhythm and a heart rate of 88 beats/min, the arterial blood pressure was 120/70 mm Hg, and the central venous pressure was 15 cm H₂O. The pulse oximeter reading revealed a saturation of 80%, which increased to 84% when the patient was breathing oxygen. Premixed solutions of phenylephrine, nitroprusside, and esmolol were available. The patient was given 1 mg of intravenous midazolam and an

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Address correspondence to Dr. Rutter, University of Michigan Medical Center, 1500 East Medical Center Drive, Ann Arbor, MI 48109-0048.

infusion of fentanyl was started. The final induction dose was 25 $\mu\text{g/kg}$ of fentanyl. Paralysis was achieved using 8 mg of intravenous vecuronium and an intravenous lidocaine bolus of 60 mg was given before tracheal intubation, which was completed without difficulty. Ventilation was controlled to sustain normocapnia. A nasogastric tube and an esophageal stethoscope were inserted. There was no significant increase in heart rate or arterial blood pressure during induction of anesthesia. After a period of ventilation, analysis of arterial blood gases revealed a pHa of 7.4, Paco_2 of 37 mm Hg, and Pao_2 of 74 mm Hg with a saturation of 94.8%.

A large tumor of the right adrenal gland was found at surgery. Palpation produced a transient increase in arterial systolic blood pressure to 190 mm Hg, which responded to cessation of the manipulation. Concurrently, ventricular ectopic beats appeared which were treated with small doses of esmolol ($0.25 \mu\text{g/kg}$ intravenously followed by an infusion of $50 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) with rapid resolution of the arrhythmia. After the removal of the tumor, the central venous pressure and blood pressure decreased over a period of some minutes, requiring an infusion of phenylephrine and fluids to maintain a satisfactory filling pressure and arterial blood pressure.

In view of the presence of a tumor in the left adrenal gland, a biopsy specimen was taken and some bleeding was experienced around the left adrenal bed, necessitating further dissection to achieve exposure and hemostasis. Three units of packed red blood cells were given. The patient had significant cholelithiasis, and the surgeon believed that a prophylactic cholecystectomy was warranted. Surgery was then completed after which the patient was taken to the intensive care unit for further postoperative monitoring. At the end of the case, the arterial blood pressure was 115/66 mm Hg, the heart rate was 60 beats/min, the central venous pressure was 19 cm H_2O , and the urine output was in excess of 50 mL/h. The patient continued to require intravenous phenylephrine and intravenous crystalloids. Two units of packed red blood cells were transfused during the first postoperative day. The trachea was extubated on the second postoperative day; however, the patient returned to the operating room for continued bleeding on the third postoperative day. Again anesthetic management was uncomplicated. Further hemorrhage on the fourth and fifth subsequent days lead to the death of the patient.

Discussion

The purpose of this report is twofold. First, in reviewing the literature no similar case could be found, and the patient's condition gave concern that there would

be significant difficulties in anesthetic management. Subsequent intraoperative anesthetic management proved to be surprisingly easy. The mixing of systemic and pulmonary blood flow in a single artery and subsequent hypoxemia were potentially compounded by further depression of a compromised heart and failure to control both preload and afterload. The value of continuous observation of oxygenation through pulse oximetry was very much in evidence and the avoidance of drugs with histamine-releasing activity and the use of a sedative/opioid technique apparently served the patient well. There was some discussion as to the appropriate vasopressor support. Our decision to use the direct α_1 -agonist phenylephrine in a patient with limited cardiac reserve could be challenged. The use of norepinephrine with α_1 -, α_2 -, and some β -adrenergic activity may have seemed more appropriate. Given the patient's history, however, and tolerance of the procedure to the point of the tumor removal, we believed that we could use phenylephrine and only use another drug if the need arose. The patient did well initially and was tracheally extubated on the first postoperative day. However, continued hemorrhage and coagulopathy compromised the patient's outcome, leading to her death on the fifth postoperative day.

Our second reason for wanting to draw attention to this case stems from information obtained in the literature search. This indicates that there may be a causal relationship between cyanotic congenital heart disease and the development of neuroblastic tumors. Folger et al. in 1964 (1) and Reynolds and Gilchrist subsequently in 1966 (2) pointed out that there may be an increased incidence of pheochromocytoma in patients with congenital heart disease. In response to an article, Miller (3) suggested in a letter to the editor in 1968 that there may be a relationship between cyanotic congenital heart disease and the development of peripheral neuroblastic tumors. Delamonte et al. (4) reviewed the autopsy results at the Johns Hopkins Institute between the years 1889 and 1982. Of 43,267 cases on the files, there were 2096 cases of congenital heart disease of which 1240 had cyanotic heart disease. There were 118 cases of peripheral neuroblastic tumors of which 39 were pheochromocytoma. Among the 118 cases of peripheral neuroblastic tumor there were 15 cases (12.7%) with congenital heart disease. Of the 39 cases of pheochromocytoma, six of the patients had cyanotic congenital heart disease. The frequency of congenital heart disease among patients with peripheral neuroblastic tumors was more than twice the frequency of congenital heart disease in the remaining autopsy population (4.8%), which was highly significant. In addition, 87% of cardiac malformations associated with peripheral neuroblastic tumors produced cyanosis

Anesthetic Management of a Child With Methylmalonyl-Coenzyme A Mutase Deficiency

Sam R. Sharar, MD, Charles M. Haberkern, MD, Rhona Jack, PhD, and C. Ronald Scott, MD

Departments of Anesthesiology, Pediatrics, and Laboratory Medicine, University of Washington, and Children's Hospital and Medical Center, Seattle, Washington

Methylmalonyl-coenzyme A (MM-CoA) mutase deficiency is one of four inborn errors in branched-chain amino acid metabolism that may result in the formation of methylmalonic acidemia. This enzyme converts propionyl-CoA (formed by the degradation of valine, isoleucine, methionine, threonine, cholesterol, and some fatty acids) to succinyl-CoA. When MM-CoA mutase is deficient, its substrate (MM-CoA) is converted to methylmalonic acid. At times of increased protein catabolism (e.g., sepsis, intestinal absorption of heme pigments, perioperative starvation, or stress), patients with MM-CoA mutase deficiency can develop severe metabolic acidosis, ketosis, and hyperammonemia.

We report the case of an 11-yr-old child with MM-CoA mutase deficiency who required general anesthesia for the resection of a large, benign maxillary tumor. We describe our anesthetic management of the patient, the results of serial analysis of arterial blood gases and chemistries, and the general anesthetic considerations for a patient with methylmalonic acidemia. Our data indicate that despite normal values of pHa, P_{aCO_2} , and anion gap, methylmalonic acid levels increased during the course of the procedure.

Case Report

The patient was an active, 23-kg, 11-yr-old girl with previously diagnosed MM-CoA mutase deficiency, chronic renal insufficiency, secondary hyperparathyroidism, and uremia-associated coagulopathy. She had a history of recurrent episodes of metabolic acidosis and seizures as an infant and toddler, but none in the preceding 2 yr. She was admitted for resection of a 4-cm-diameter, benign, giant cell bone granuloma of her left maxilla, a tumor that en-

croached on the oropharynx and the left naris to the midline septum, and that protruded anteriorly such that lip closure was not possible. Preoperatively, she received a low protein diet ($1 \text{ g} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$) and daily oral citrate therapy equivalent to 120 mEq of bicarbonate in four divided doses to counteract the effects of her usual methylmalonic acid generation and to maintain a normal pHa. Eight hours before surgery, oral intake was curtailed, and maintenance intravenous infusion of 5% dextrose and hypotonic saline containing sodium bicarbonate (50 mEq/L) was begun. On the morning of surgery, she received both cryoprecipitate and $7 \mu\text{g}$ desmopressin intravenously to reverse her coagulopathy.

Anesthesia was induced intravenously with $100 \mu\text{g}$ of fentanyl, 200 mg of sodium thiamylal, and 10 mg of atracurium. An oral endotracheal tube was easily inserted, and both a urinary catheter and arterial catheter were placed. In addition, an orogastric tube and a throat pack were placed to prevent the passage of blood into the gut and its attendant protein absorption. Anesthesia was maintained with 1% isoflurane in oxygen with incremental intravenous injections of fentanyl and atracurium. Ventilation was controlled with a tidal volume of 15 mL/kg at a rate of 10 breaths/min to achieve a stable end-tidal CO_2 of approximately 30 mm Hg. Arterial blood pressure, heart rate, and temperature did not vary more than 15% at any time during the course of the anesthetic. The intravenous bicarbonate infusion used preoperatively was continued throughout surgery until oral intake was begun on the third postoperative day.

The procedure, including excision and curettage of the mass, maxillary reconstruction, and tooth extractions, required 130 min of anesthesia time and was uneventful. Intravenous fluid therapy included 850 mL of lactated Ringer's solution plus 100 mL of bicarbonated maintenance solution. Estimated blood loss was 350 mL and total urine output was 300 mL. After reversal of neuromuscular blockade with intravenous administration of 25 mg of edrophonium and 0.2 mg of atropine and following awake tracheal

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Address correspondence to Dr. Sharar, Department of Anesthesiology, Children's Hospital and Medical Center, P. O. Box C5371, Seattle, WA 98105.

Table 1. Analysis of Arterial Blood Gases and Chemistries

Test	Preop	Intraop	PAR	Postop
Arterial pH (7.35-7.45)	7.37	7.45	7.34	—
CO ₂ (mmol/L) (22-30)	30	26	25	35
AG (mEq/cL) (8-22)	25.2	16.8	17.8	20.1
NH ₃ (μmol/L) (8-54)	50	29	34	37
MMA (μg/mL) (undetectable)	115	146	167	125

CO₂, serum bicarbonate; AG, anion gap; NH₃, serum ammonia; MMA, plasma methylmalonic acid.

Data are presented for the perioperative period, with the normal range for each test stated in parentheses. Data are shown for the night before surgery (Preop); 60 min into the procedure (Intraop); upon arrival in the postanesthetic recovery room, 130 min after induction (PAR); and the first postoperative day, 24 h after induction (Postop).

extubation, the patient recovered without incident and returned to the ward where she received patient-controlled morphine analgesia.

Serial blood measurements were made of arterial pH, CO₂ content, anion gap, and ammonia, as well as plasma methylmalonic acid levels (Table 1). In addition, levels of serum electrolytes and glucose were measured, and they remained within the normal range. Blood samples for measurements of methylmalonic acid were analyzed by gas chromatography/mass spectrometry. The procedure is routinely used in organic acid analysis (1). One milliliter of plasma was alkalized and a primary derivative was made with hydroxylamine. The sample was subsequently acidified and organic acids were extracted with ethylacetate and ether. The organic phase was dried under nitrogen and derivatized with BSTFA (Pierce Chemical, Rockford, Ill.) to form a trimethylsilyl derivative. The derivatized compounds were injected into a Hewlett Packard gas chromatograph/mass spectrometer. Methylmalonic acid was identified in patient samples on the basis of retention time and computer match with a library mass spectrum for methylmalonic acid. Peak areas were compared between patient samples and a 250-μg/mL standard for quantitation.

Discussion

Methylmalonyl-CoA mutase deficiency is a rare but well-described (2,3) defect in protein metabolism that is inherited as an autosomal recessive trait. Methylmalonyl-CoA mutase requires a vitamin B₁₂ coenzyme (adenosylcobalamin) as a cofactor for normal activity. The clinical syndrome of methylmalonic acidemia results from abnormalities of either the mu-

tase protein or the synthesis of the B₁₂ cofactor and occurs in approximately 1:48,000 infants (4). At times of increased protein metabolism, plasma methylmalonic acid levels, undetectable in normal subjects, may reach levels of 26-340 μg/mL (5). Patients may present with lethargy, recurrent vomiting, dehydration, respiratory distress, metabolic acidosis, ketonemia, and hyperammonemia. Acute treatment for the syndrome consists of improving intravascular volume with intravenous crystalloid administration, coupled with treatment of the acidosis with intravenous sodium bicarbonate. Long-term therapy includes a reduction in dietary protein intake, supplemental bicarbonate or citrate, and supplemental cobalamin.

Surgery presents several problems for patients with methylmalonic acidemia. First, a period of starvation and protein catabolism is imposed beginning the night before surgery and extending for a variable period postoperatively. Second, procedures associated with bleeding and involving the oropharynx, nasopharynx, or upper gastrointestinal tract, especially in patients with coagulopathy, may increase the incidence of heme pigment absorption across intestinal epithelium and impose an additional protein load for catabolism. Third, tissue breakdown associated with both the surgical procedure and the stress response may exacerbate protein catabolism. Fourth, anesthetics may influence amino acid metabolism resulting in increased methylmalonic acid levels. A known example is nitrous oxide, which reduces the activity of methionine synthetase, a methyl-B₁₂-dependent enzyme. Rask et al. (6) have shown that 24 h of nitrous oxide exposure increased the levels of urinary methylmalonic acid threefold in patients with normal protein metabolism. This increase is most likely a consequence of nitrous oxide inhibition of the cobalamin coenzyme similar to its inhibition of methionine synthetase (7) and may have consequences in a patient susceptible to methylmalonic acidemia.

Using our patient as a case study, the anesthetic management of a patient at risk for methylmalonic acidemia should address each of these points. The impact of the preoperative starvation period may be lessened by decreasing its duration to 3 h, a practice that has been shown not to increase the risk for perioperative aspiration of gastric contents (8,9), and by the generous use of intravenous fluids and dextrose to minimize both hypovolemia and protein catabolism. All preoperative medications relating to the abnormal MM-CoA mutase/coenzyme complex (e.g., bicarbonate or cobalamin supplementation) should be continued perioperatively. In the operating room, monitors to evaluate intravascular volume status and tissue perfusion (e.g., urinary catheter, central venous catheter, and/or arterial catheter) should

be placed. If the procedure potentially involves intestinal exposure to blood, both an orogastric tube and throat pack should be placed to reduce absorption of heme proteins, and known coagulopathies should be corrected. Serial analysis of arterial blood gases and plasma levels of electrolytes, glucose, and ammonia should be conducted to help detect the onset of acidosis or hyperammonemia so that abnormal changes may be treated. Finally, although the adverse effects of nitrous oxide on patients with abnormal MM-CoA mutase activity are theoretical and have not been studied, it seems prudent to avoid this anesthetic in patients at risk for methylmalonic acidemia.

Our patient had a clinically uneventful anesthetic and operative procedure, and all of her blood chemistries except for the organic acid assays remained normal throughout the perioperative period. Values of methylmalonate in the 30–50 $\mu\text{g/mL}$ range will influence electrolyte balance and require bicarbonate therapy to maintain a normal pHa. Although this patient's methylmalonic acid levels before hospitalization were not known, her high preoperative methylmalonic acid level (115 $\mu\text{g/mL}$) continued to increase during surgery and reached a peak (167 $\mu\text{g/mL}$) at the time of her arrival in the recovery room. Within 18 h, however, the level returned to its preoperative value without intervention, despite the presence of continued fasting postoperatively.

These observations have several implications. First, some undefined factors relating to our anesthetic, the conduct of the operative procedure, and/or changes in the patient's intraoperative metabolism resulted in an increase in methylmalonic acid concentration. It appears that starvation alone is not responsible, as fasting continued for 2 days postoperatively during which time the methylmalonate level returned to its preoperative value. The cause of this fluctuation is unclear, but probably it is related to modified intraoperative protein catabolism that is modulated by stress hormones (e.g., insulin, cortisol, or catecholamines). Both isoflurane (by increasing insulin secretion [10]) and clonidine (by reducing the catecholamine response to anesthesia and surgery [11]) may have potential beneficial effects in these patients. Second, analysis of arterial blood gases and pHa are not sensitive enough to detect an increase in this specific organic acid. Had this operative procedure been more lengthy or resulted in further elevations of methylmalonic acid, abnormalities in ammonia or other blood chemistries and progressive acidosis may have been detected. Finally, although this patient

was clinically stable at the same time that the organic acid level was rising, one cannot assume that a stable clinical picture precludes potentially problematic chemical changes.

In conclusion, we have presented a case of general anesthesia for an elective surgical procedure in a child with known MM-CoA mutase deficiency and a history of methylmalonic acidemia. Guidelines are suggested to address pertinent anesthetic considerations, including perioperative fasting, intravascular fluid management, intraoperative monitoring, and anesthetic agents. Serial methylmalonic acid levels measured in this case suggest that a surgical procedure or general anesthetic may increase the rate of methylmalonate formation in a patient who is metabolically and clinically well controlled. The anesthesiologist needs to be aware of the danger of organic acidemia developing in patients with this congenital defect even though this did not occur in the present case.

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Letters to the Editor

Prevention of Tachycardia and Hypertension Associated With Tracheal Intubation

To the Editor:

In their study comparing esmolol, lidocaine, and fentanyl, Helfman et al. (1) conclude that only esmolol reliably attenuates the hypertension and tachycardia associated with tracheal intubation. The manner in which esmolol was compared with lidocaine and fentanyl merits further comment.

When claiming that lidocaine "has been found to be only inconsistently effective in preventing cardiovascular changes associated with tracheal intubation," the authors are being generous. In fact, there is an abundance of evidence testifying to its lack of effect (2-7). Laurito et al. (5) have already suggested that the use of lidocaine for this purpose should be abandoned.

Helfman et al. used 200 μg of fentanyl in their study, quoting two studies in which fentanyl was used at doses of 1.5 and 3 $\mu\text{g}/\text{kg}$ to attenuate the cardiovascular responses to intubation (8,9). However, both these studies were performed on geriatric patients, known to be more sensitive to this (and other) anesthetic agents. Other studies have indicated that at least 5 $\mu\text{g}/\text{kg}$ of fentanyl is required to attenuate successfully these reflexes in the young or middle aged (10-14).

Clearly fentanyl used at this dosage may result in an unacceptably high incidence of complications—notably hypotension and respiratory depression. In this respect, alfentanil may offer distinct advantages over fentanyl and has already been demonstrated to successfully attenuate hypertension and tachycardia on intubation (13,15). Although Black et al. (13) concluded that a dose of 30 $\mu\text{g}/\text{kg}$ was required to achieve this aim, Crawford et al. (15) have since demonstrated that 10 $\mu\text{g}/\text{kg}$ may be sufficient if non-vagolytic neuromuscular blocking agents are used.

Peter C. Stride, FFARCS
Department of Anesthesiology
University of Texas Medical Branch
Galveston, TX 77550-2778

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To the Editor:

The study by Dr. Helfman and associates (1) offers evidence to aid in resolving a long-standing clinical controversy. For years, debate concerning the most useful technique for minimizing the hyperdynamic circulatory responses to laryngoscopy and intubation has focused on the use of various pharmacologic agents as adjuncts to general anesthetic drugs. These include opioids, local anesthetics, and adrenergic receptor blocking agents. Of the latter group, one might expect that the unique pharmacologic properties of esmolol would render it ideally suited to the task.

The data of Helfman et al. (1) purport to confirm this hypothesis. Comparing the use of esmolol with fentanyl, lidocaine, or placebo given during a general anesthesia induction sequence, the authors found that only esmolol "provided consistent and reliable protection against increases in both heart rate and . . . blood pressure" after laryngoscopy and intubation. However, the methodology chosen by the authors may have resulted in an unfair comparison.

Their protocol utilized the following sequence: induction with thiopental, injection of study drug, injection of succinylcholine, followed by laryngoscopy and intubation performed 2 min after induction. This sequence might be

expected to favor the effectiveness of esmolol which has an onset of action known to be very rapid (2,3).

In contrast, lidocaine has been shown in a prospective, randomized study to blunt hemodynamic reflexes when given 3 min before laryngoscopy, but not 1, 2, or 5 min before (4). No similar investigation has been performed to determine the optimal timing of fentanyl administration with respect to laryngoscopy. However, a series of elegant studies have been conducted by investigators at Stanford (5-7) using sophisticated pharmacokinetic-pharmacodynamic modeling techniques designed to predict changes in brain concentration of narcotics over time after intravenous injection. Their model predicts a peak brain concentration of fentanyl at 3.6 min after intravenous bolus (7). Thus, as with lidocaine, one must conclude that the principal benefit of fentanyl was not realized in the time frame used by Helfman et al. in their protocol.

The study design used by these authors resembles that used in a recent study by a different group of investigators (8), which compared the use of alfentanil, lidocaine, and placebo in attenuating laryngoscopy-associated cardiovascular reflexes. Those authors also administered their study drugs between induction and laryngoscopy and concluded that alfentanil is effective but lidocaine is not. A subsequent letter to the editor (9) criticized these authors' findings by questioning whether their methodology may have introduced a bias in favor of alfentanil.

At length, further reflection appears merited. To be sure, a similar criticism could be made concerning the protocol chosen by Helfman et al. (1). Given what is known about the differential pharmacokinetics and dynamics of the drugs they chose to compare—fentanyl, lidocaine, and esmolol—their administration after intravenous induction biases the results in favor of esmolol. Nonetheless, perhaps our practice is now sufficiently advanced that, with the vast array of modern pharmaceuticals available for clinical use, the question regarding the comparative utility of adjunctive drugs in helping to control hemodynamic responses to noxious stimuli needs to be rephrased. Rather than "Which drug [best] prevents tachycardia and hypertension associated with tracheal intubation" as posed by Helfman et al. in the title of their report, the better question might be "Which drug offers its benefit *most rapidly* and for the *shortest duration*?"

The *ultimate* effectiveness of one or another agent—the issue on which previous studies have focused—is difficult to assess in an unbiased fashion because of the varying time-courses of action that different classes of drugs feature. At present, however, this appears to be a moot point; why rely on agents that require a time delay to yield a result when newer ones are available whose effects are more immediate? The data offered by Helfman et al. (1) have not necessarily demonstrated that esmolol is "better" but rather that it is *faster*, which, in itself, is a potent advantage.

Robert F. Atkins, MD
Temple University School of Medicine
Philadelphia, PA 19140
and
Department of Anesthesiology
Abington Memorial Hospital
Abington, PA 19001

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In Response:

We thank Dr. Stride for constructive comments and agree that lidocaine is virtually ineffective in preventing cardiovascular changes after endotracheal intubation. This does depend on dose and timing. It is precisely for this reason that we studied lidocaine, fentanyl, esmolol, and placebo in a double-blind protocol. We arbitrarily used a single dose of each drug at a specific time before intubation. Both dose and time for each drug corresponded to clinical practice and to what was in the recent literature (1,2).

Fentanyl was used at a 2.5- μ g/kg dose—and this is a compromise but one that is clinically appropriate. We consider our study population, although not geriatric (average age 50 yr) to be close to it, and we did wish to avoid respiratory depression and hypotension. We did not study alfentanil, but we do invite Dr. Stride to do this.

Most important, we caution Dr. Stride, who quotes many investigations alluding to how our results could have been improved, not to draw conclusions. Different doses of drugs in different patients, studied according to different protocols, lead to incomparable results. As lidocaine in any dose is inconsistent and higher doses of fentanyl (3) create unacceptable side effects, we maintain as a result of our study, that 150 mg of esmolol is the safest, most efficacious attenuator of the hemodynamic consequences of intubation.

We thank Dr. Atkins for his astute and scholarly comments, with which we generally agree. Dr. Atkins, however, states that we have chosen an unfair methodology resulting in an unfair comparison, biasing the data in favor of esmolol. We could not disagree more.

We know that esmolol must be given after (not before) induction approximately 2 min before intubation (1,2). Lidocaine in any time frame is inconsistently effective (4,5). We did use a higher dose of lidocaine than usual (2.5 mg/kg) and we did encounter significant attenuation of systolic blood pressure. The Stanford data are of course fundamental, but we caution Dr. Atkins that this information came from models, not humans, and that brain con-

centration is not heart or effector-site concentration. Most important, Tables 1 and 2 of our paper yield data out to 10 min after intubation—not 2 min. The same conclusions stand in favor of esmolol, without a time bias! Yes, esmolol does work faster, it lasts almost as long, and as it attenuates both heart rate and systolic blood pressure, it is better.

Finally, the Pathak-Alfentanil study is inconsequential to Dr. Atkins' argument. Different drugs (no esmolol), different doses, different patients, and different protocols were used, and the study design was not similar; their conclusions neither support nor debunk our data. Dr. Atkins wrote a letter to the editor in response to Dr. Pathak's investigation and he suggests that a bias exists in favor of alfentanil, just as he does above with our study biasing esmolol. Perhaps something seems to pique his interest on this subject, inviting him to write bias letters?

And finally, we disagree that esmolol "offers the benefit most rapidly and for the shortest duration." Again, Tables 1 and 2 record the data to 12 min and not 2 min. Only esmolol and not placebo or lidocaine or fentanyl provided consistent and reliable protection against increases in both heart rate and systolic blood pressure accompanying laryngoscopy and tracheal intubation.

Steven M. Helfman, MD
Martin I. Gold, MD
Everard A. deLisser, MD
Claire A. Herrington, RN
Department of Anesthesiology (R-370)
University of Miami School of Medicine
P.O. Box 016370
Miami, FL 33101

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Cerebral Circulation and Oxygen Uptake Parallels

To the Editor:

I read with interest the well-constructed study by Prough and coworkers (1). Their findings regarding the cerebral circulation and oxygen uptake parallels, for the most part, that which occurs on a global scale with the systemic circulation and oxygen uptake (2,3). There is a progressive vasoconstriction during hypothermic cardiopulmonary bypass, yet systemic oxygen uptake remains unchanged. From the study of Prough and colleagues (1), it is reasonable to assume that the cerebral circulation is not immune

from the pathophysiological process that affects the circulation as a whole.

Also worthy of comparison is the interaction that Prough and colleagues found between arterial carbon dioxide tension and temporal stage during cardiopulmonary bypass on cerebral hemodynamics, which also occurs in the systemic circulation (2). However, it is here that the findings diverge as the systemic circulation becomes progressively more responsive to carbon dioxide tension (2), whereas Prough and coworkers found a decrease in responsiveness in the cerebral circulation (1). I wonder whether this discrepancy in findings may be due to Prough and colleagues not mathematically correcting their data for the progressive cerebral vasoconstriction that they have documented?

R. Peter Alston, MD, FCAaes
Department of Anesthesiology
University of Washington
Seattle, WA 98195

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In Response:

We appreciate the thoughtful comments on our study by Dr. Alston (1). In fact, our data do suggest that the cerebral circulation undergoes progressive vasoconstriction while cerebral oxygen consumption remains unchanged. The similarity between those observations and the observations reported from their laboratory is striking (2,3). We can only speculate on the pathophysiologic mechanism of the increase in cerebrovascular resistance. However, we suspect that it may be related either to primary microembolic obstruction of the cerebral microvasculature (4) or to active vasoconstriction resulting from that obstruction. Because of the large number of patients who undergo cardiac surgery and the high incidence of neuropsychologic sequelae of cardiac surgery, further clarification of the mechanisms and prevention of progressive cerebral vasoconstriction are imperative.

However, we would like to clarify one aspect of our data that apparently has been confusing. We have no information regarding changes in the responsiveness of the cerebral circulation to carbon dioxide as a function of the duration of cardiopulmonary bypass. Our data demonstrate only that the time-dependent decrease in cerebral blood flow tends to accentuate the cerebral vasoconstriction resulting from a decrease in carbon dioxide tension while minimizing the increase in cerebral blood flow that accompanies an increase in carbon dioxide tension. Because each measurement of cerebral blood flow using xenon clearance requires approximately 15 min, we are unable to evaluate cerebrovascular responsivity to carbon dioxide tension as a function of time during stable cardiopulmonary bypass.

Therefore, we believe there is no discrepancy between our cerebral circulatory data and the systemic circulatory data from Dr. Alston's laboratory.

Donald S. Prough, MD
Department of Anesthesia
Section on Critical Care
The Bowman Gray School of Medicine
Medical Center Boulevard
Winston-Salem, NC 27157-1009

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Bupivacaine Toxicity After Stellate Ganglion Block

To the Editor:

Wulf et al. (1) reported that approximately 30% of their patients exhibited toxic plasma levels of bupivacaine (0.5% bupivacaine, 10 mL) after stellate ganglion block (SGB). A 100% incidence of sympathectomy was also observed. They make recommendations that are timely and appropriate concerning monitoring, intravenous access, and resuscitation issues. In a survey we performed, 44% of pain clinics placed an intravenous line before SGB and only 37% required NPO status (2). However, the question their report raises is whether 50 mg of bupivacaine is necessary for a successful SGB.

Hardy (3) has shown that 20 mL of 0.0125% bupivacaine (2.5 mg total dose) produced an effective SGB in all three patients tested. Increasing the concentration 10-fold (0.125%) would present a total dose of 25 mg and should not result in toxic levels according to Wulf et al. (1). In another study, 10 mL of bupivacaine was adequate for cranial and high cervical sympathectomy, but 20 mL was required for consistent sympathectomy of the upper extremity (4). It appears that decreasing the concentration of bupivacaine and perhaps increasing the volume of drug delivered will ensure an adequate block and prevent toxic levels.

Although a higher concentration of bupivacaine (0.5%) may increase the duration of the block, an unacceptable rate of systemic toxicity results. Other techniques to provide for long-term blockade, such as the use of indwelling catheters, should be considered instead. In our clinic, we have used 10 mL of 0.25% bupivacaine with excellent results and without obvious signs of toxicity.

We would add to Wulf's recommendations:

6. Patients should be NPO before stellate ganglion block.

7. The appropriate concentration and volume of bupivacaine should be used. A cranial sympathectomy can be performed with 10 mL of 0.125%–0.25% bupivacaine. Upper extremity sympathectomy can be performed with up to 20 mL of 0.0625%–0.125% bupivacaine.

Mark E. Romanoff, MD
Jay S. Ellis, Jr., MD
Pain Management Clinic
Department of Anesthesiology/SGHSA
Wilford Hall USAF Medical Center
Lackland AFB, TX 78236

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In Response:

We would like to thank Drs. Romanoff and Ellis for their additional recommendations. We agree that 10–20 mL of 0.125%–0.25% bupivacaine will usually result in sufficient sympathetic blockade, but the recommendations in the current literature are somewhat diverse: "weak local anesthetic" concentration (1), 0.5% bupivacaine (2,3), 0.75% bupivacaine (4). Nevertheless, even with a reduced concentration and dose of a local anesthetic, an inadvertent subarachnoid or intraarterial injection will lead to significant complications.

In a survey we performed in western Germany last year, more than 44,000 stellate ganglion blockades from 38 departments were reviewed. The incidence of severe complications (requiring treatment) was as follows:

Convulsions	34	(0.76 in 1000 blocks)
Other central nervous system symptoms	16	(0.36 in 1000 blocks)
Subarachnoid anesthesia	6	(0.13 in 1000 blocks)
Epidural anesthesia	3	(0.07 in 1000 blocks)
Pneumothorax	9	(0.20 in 1000 blocks)
Allergic reactions	2	(0.05 in 1000 blocks)
Other	5	(0.11 in 1000 blocks)
Total	75	(1.7 in 1000 blocks)

Drs. Romanoff and Ellis state that, in 1988, 44% of U.S. pain clinics placed an intravenous line for stellate ganglion blockade. In 1990, the following measures of precaution were standard in Germany (percentage of departments):

Intravenous access	72%
Test dose	53%
Aspiration tests	100%
Assistant person	73%
Anticonvulsive drugs at hand	73%
Equipment for intubation	94%
Electrocardiographic monitoring	28%

The majority of dangerous complications of stellate ganglion blockade are not caused by the needle, but by the local anesthetic injected. Therefore, the risk could be re-

duced by a change to the application of very low doses of opioids (e.g., 0.03 mg of buprenorphine). The most severe side effect with this technique has been one case of temporary itching in almost 1000 injections performed in our pain clinic. Even in the case of inadvertent intravascular or subarachnoid injection, no life-threatening complications have to be expected (5,6). According to preliminary results, the analgetic effect seems to be at least as good as with local anesthetic blocks (7). We, therefore, have changed our practice of stellate ganglion blockade to low-dose opioid injections, except for patients in whom a distinct vasodilatory effect is wanted.

Hinnerk Wulf, MD

Christoph Maier, MD

Hans Albrecht Schele, MD

Department of Anesthesiology

Klinikum der Christian-Albrechts-Universität zu Kiel

Arnold-Heller Strasse 7

2300 Kiel, Germany

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Hyperacusis After Spinal Anesthesia

To the Editor:

Fog et al. (1) found hearing changes after spinal anesthesia, possibly mediated by the transmission of decreased cerebrospinal fluid pressure to the cochlea and subsequent endolymphatic hydrops; however, they did not describe the mechanism. Lee (2) suggests that decreased labyrinthine pressure per se rather than hydrops was responsible. Hardy (3) was initially quite dismissive of the low pressure/hydrops theory but later (4) described two patients after spinal puncture with auditory symptoms from low and not high intracranial pressure.

Fog et al. saw improved hearing in some patients. Although hard to explain, this has often been reported in various disorders and strongly backs the hydrops theory: indeed, I predicted in advance (5) that such hyperacusis would occur. Manipulation of respiratory gases can also lead to hyperacusis (6). Careful studies on experienced subjects showed that hyperventilation first depressed the hearing but then restored it beyond normal limits. These aftereffects coincide with reduced cerebrospinal fluid pressures.

Overrecruitment (where at high-intensity levels tones of equal intensity evoke a louder sensation in the impaired ear

than the normal one) is the first manifestation of Meniere's disease, preceding hearing loss (7). I prefer to call this sensation audiosensitivity (8) or aversion to a television, radio, or record player such that the person needs to turn down the volume. It is presumably the same as "post-puncture cerebral phenomena (hyperacusis, irritability, etc)" briefly noted by Masserman (9). Although I had predicted it (5), this is the first time I have seen audiosensitivity mentioned after lumbar puncture. No doubt it is commonly ignored by both patients and doctors.

Fog et al. were quite rightly concerned at the lack of explanation for unilateral changes in their studies and in Meniere's disease. However, I have found that bilateral signs of early hydrops are the rule in clinically unilateral cases. I have retrieved at random from my files routine impedance test results on nine ENT outpatients with symptoms of hydrops or Meniere's disease confined to one ear, with normal middle ear pressures and compliances and with no pure-tone hearing loss in the good ear. Seven patients had bilateral middle-ear reflex abnormalities of the types found in patients with audiosensitivity (8). One had bilaterally normal stapedial reflexes. Only one had a unilateral reflex abnormality (lowered reflex thresholds with sound into bad ear only). Incidentally, in two patients, hearing in the bad ear fluctuated to excellent levels of -10 dB hearing level (International Standards Organization), indicating hyperacusis.

I hope that anesthesiologists continue researching this area. Not only could otovestibular symptoms be used for spinal fluid pressure monitoring, but the long-standing controversy and confusion over intracranial hydrodynamics (9) could be resolved, shedding new light on hydrops and the initiation of Meniere's disease (10).

A. G. Gordon

32 Love Walk

London SE5 8AD, England

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In Response:

We are thankful to Dr. Gordon for his kind interest. We agree that spinal fluid pressure changes could cause audio-vestibular symptoms and that this is of interest for further research. We think that there is a relationship between hearing changes and lumbar puncture and that hearing

losses are a more sensitive instrument to monitor spinal fluid pressure changes than headache is.

However, there is evidence that if the hearing loss is large enough it is also accompanied by headache. In one patient, we have seen a bilateral hearing loss most pronounced on the right side. This was accompanied by a typical spinal headache. After blood patch, the headache disappeared and the hearing returned to normal.

Albert Sundberg, MD, PhD
Department of Anesthesia
Eksjö-Nässjö Hospital
S-575 28 Eksjö, Sweden

A Method to Assess Correct Endotracheal Tube Placement

To the Editor:

The method for confirmation of tracheal intubation must be simple, rapid, and effective as reported by Ian Smith (1).

The esophageal detector device described by Wee (2), consisting of a 60-mL syringe that is fitted by way of an adaptor over the end of an endotracheal tube, is a simple, rapid, and effective method. This was confirmed in a blind, randomized study in which 40 patients had both their trachea and esophagus intubated (3).

An even simpler method is auscultation over the epigastrium, then in the right and the left axilla. This method is reliable, easily applied, and inexpensive (3).

Knud H. Andersen, MD
Department of Anaesthetics
Bispebjerg Hospital
Bispebjerg Bakke 23
2400 Copenhagen, Denmark

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Causalgia Induced by Telephone-Mediated Lightning Electrical Injury and Treated by Interpleural Block

To the Editor:

About 1000 people in the United States, 50 people in Sweden, and 7 per million in Canada die as a result of household and commercial electrical injury each year (1,2). An additional 300 people die and more than 1000 are injured by lightning in the United States. The lightning in a thunderstorm can cause electrical shock through telephone wires. Each year two telephone users die in the United States because of electrical shock during a thunderstorm

and hundreds are injured all over the world (2). We report two telephone operators in whom severe causalgia developed after being struck by lightning through their headphones and who were successfully treated with interpleural block. Two young women, 30- and 32-yr-old Southern Bell operators who worked next to each other, were struck by lightning through their headphones on July 26, 1989 at the time of a severe thunderstorm. They felt the sudden electric shock passing through their bodies. Most of it passed from their heads to their right arms. They felt as if "someone had hit them with a baseball bat." Their right arms turned purple, became painful, and developed a burning sensation immediately after the electrical shock.

They were treated by emergency room and other physicians with pain medications, antidepressants, physical therapy, and transcutaneous electrical nerve stimulation. Six months later, their arms were still swollen, had a burning sensation, and ached and their ring and little fingers were numb. Exposure to cold and heat increased the pain. The entire right arm felt as if it was being twisted, tight, and throbbing. They exhibited symptoms indicative of psychological problems and experienced occasional dizziness and headaches. On examination, the arms and the forearms were swollen, cold, and tender to touch. Both of them had allodynia, hyperpathia, dysesthesia, and hyperalgesia with some vasomotor and pseudomotor changes. Right shoulder muscles were taut and tender and their heads were slightly tilted to the right side.

Interpleural blocks were done at the right fourth intercostal space about 6 cm from the spinous process (3). The patients were placed on their backs in the 30° Trendelenburg position. Thirty milliliters of 0.25% bupivacaine with 1 in 5 μ g/mL of epinephrine was injected through the interpleural catheter. The patients were left in that position for 45 min. Both of them developed Horner's syndrome within 15 min after the injection, indicating the ocular sympathetic palsy (T1). The burning sensation and the pain in the hand were considerably reduced. Their right hand grip improved. The skin became red and warm. The patients were able to move their upper arms and heads without much discomfort. They were sent to the floor for physical and occupational therapy. The patients received 30 mL of 0.25% bupivacaine with 1 in 5 μ g/mL of epinephrine through the interpleural catheter in the above described position every day for 1 wk. They were sent to physical and occupational therapy 1 h after an injection of local anesthetic. Patients showed 90% relief after 1 wk of therapy and were discharged from the hospital. Both of them returned to work after 3 wk of physical therapy, occupational therapy, psychotherapy, and biofeedback.

The treatment was based on previous experience in treating reflex sympathetic dystrophy that failed to respond to stellate ganglion blocks. The interpleural blocks helped these patients by producing profound blockage of the sympathetics to the upper extremity, head, and neck, as well as the upper intercostal and the lower brachial plexus somatic nerves.

T. R. Shantha, MD, PhD
Department of Anesthesiology
Georgia Baptist Medical Center
and Medical College of Georgia
300 Boulevard, NE
Atlanta, GA 30312

T. R. Shantha has published previously under the name T. R. Shanthaveerappa.

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Near Mishap in Drug Administration Due to Similarity Between Drug Packaging

To the Editor:

The unintended administration of drugs by anesthesiologists in the perioperative period represents preventable incidents related to human error. Cooper et al. (1) reported that 19% of preventable incidents in the operating room by anesthesiologists were related to the accidental exchange of syringes containing anesthetic drugs. The most frequently reported syringe interchange was with muscle relaxants and their antagonists. Factors that were thought to contribute to the syringe swap problem were the similarities of size, labeling, and color. In another study (2), which analyzed the incidence of major errors in anesthesia management, drug ampule swap was responsible for 4.1% of anesthetic incidents.

Many drug manufacturers are aware of this problem and have made a concerted effort to package their drugs in such a way that they can be easily identified from the shape, color, or labeling of the container. Manufacturers of neuromuscular blocking drugs have packaged their drugs in containers that make them easily identifiable. Examples of different packaging techniques are the square bottles in which succinylcholine is contained and the hexagonal-shaped containers for atracurium. Another group of drugs that deserve unique packaging for identification are vasoactive drugs. We recently avoided a potential catastrophic patient outcome involving a sympathomimetic drug.

Multiple drugs are stocked in our anesthesia workroom. Two of these drugs are protamine sulfate (Lypomed, Rosemont, Ill., Figure 1) and dopamine HCl (American Regent Laboratories, Shirley, N.Y., Figure 1). Before coronary artery bypass surgery in our institution, the anesthesiologist routinely stops in the anesthesia workroom to select drugs that will be used during the patient's anesthetic. In this case, several vials of protamine sulfate were obtained from the anesthesia workroom. Before the termination of cardiopulmonary bypass, protamine sulfate was drawn up from the ampules into a 20-mL syringe. During the aspiration of the protamine sulfate from these vials, it was noticed that two of the ampules, which had an appearance similar to the protamine sulfate vials, were actually vials of dopamine HCl. Despite a thorough investigation, it could not be determined how vials containing dopamine were intermixed with vials containing protamine sulfate. Although a vigilant anesthesiologist is the best and ultimate protector against this type of mishap, it would be helpful if

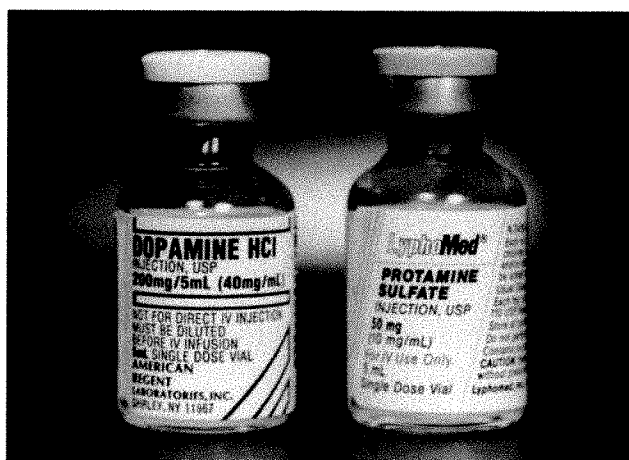


Figure 1. Similar appearance of protamine sulfate and dopamine HCl vials.

pharmaceutical companies would package potent vasoactive drugs in distinctive containers to help prevent the unintended injection of potentially harmful medication.

Juraj Sprung, MD, PhD
Eugene Y. Cheng, MD
Department of Anesthesiology
Froedtert Memorial Lutheran Hospital
9200 West Wisconsin Avenue
Milwaukee, WI 53226

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A Simple Method to Retrieve Irretrievable Epidural Catheters

To the Editor:

There are case reports of breakage and irretrievable epidural and spinal catheters after continuous epidural, caudal, and spinal anesthesia (1-8). In some of the cases, the broken ends of the catheters were removed surgically (1,2). There is already a report of two broken microspinal catheters out of 58 continuous spinals. Broken catheters were left in the subarachnoid space (5). This letter describes a simple method to retrieve irretrievable catheters from the epidural space when other methods such as changing the position and flexion of the lumbar spine fail.

Our patient was an obese woman scheduled for continuous epidural anesthesia for labor and delivery. The epidural catheter (Abbot tray) was inserted at the L3-4 interspinous space while the patient was in a sitting position. A total of 15 mL of bupivacaine (0.25% with epinephrine) was injected through the epidural catheter resulting in no block. The procedure was repeated using a new epidural set. The block was not uniform, and the patient continued to experience some pain. It was decided to pull the epidural

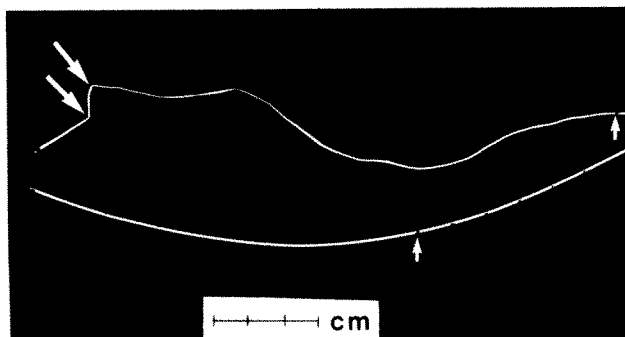


Figure 1. The *top* catheter is the retrieved catheter compared with the normal catheter (*below*). Note two kinks in the retrieved catheter (*arrows*) and how much the first catheter was stretched when force was used to pull it out (*arrow on the right side*).

catheter out and go one dermatome space higher. The last 10 cm of the catheter could not be removed. Steady force was used to pull the Teflon catheter. It stretched almost double its length from the skin. Placing the patient in the same position utilized to insert the epidural catheter and flexing the patient's lumbar spine also failed to retrieve the catheter.

A new epidural tray was opened. The irretrievable catheter and the entrance site at the skin were cleaned with alcohol and povidone iodine. A sterile Tuohy needle was passed over the epidural catheter. As it approached the skin, the catheter was pulled cephalad, applying slight tension on the catheter at 70°–80° angle to the skin surface. The epidural needle was threaded gently with the beveled surface facing cephalad. The ligamentum flavum and the epidural space were located by tactile and pressure sensations. The catheter along with the epidural needle was pulled out gently in one mass without any difficulty. Close examination revealed no shearing of the catheter, two acute kinks located 4 and 5 mm from the tip, and that the catheter was stretched from 3 to 5 cm in length (Figure 1). The next epidural was performed at the L2-3 level resulting in good analgesia.

We have successfully removed irretrievable catheters in two other cases using this method. One catheter had a knot and another catheter was kinked. In one case, the epidural needle had to be pulled back about 5 mm and reinserted twice through the ligamentum before we could retrieve the catheter.

This maneuver enlarges the hole and/or separates the elastic tissue holding the catheters. Applying slight tension on the catheter as the epidural needle is threaded prevents the slackness of the catheter being caught at the tip of the needle and prevents shearing off the catheter as the needle is advanced. Still there is a danger of shearing the catheter. This method can be attempted using blunt (by filing) needles after threading the stylet as far as it can be advanced.

Preliminary experiments on a plastic model show that the blunted epidural needle, Raczi epidural needle, and 18-gauge, 15-cm-long disposable trocar needle (from Cook—can be obtained from the radiology department) do not shear the catheter. If there are no contraindications,

biplanar image intensification radiographs can be used to monitor the movement of the needle.

T. R. Shantha, MD, PhD
Southeastern Pain Institute
College of Georgia
J. J. M. Medical College

M. Mani, MD
Department of Anesthesiology
Georgia Baptist Medical Center
300 Boulevard NE
Atlanta, GA 30312

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Capnography: Never Forget the False-Positives!

To the Editor:

Several letters in the recent anesthesia literature have again discussed the use of capnography in the detection of tracheal intubation. Edelist (1) has recently commented that we must emphasize clinical observation of the patient in the training of new anesthesiologists. We also appreciate the analysis of Dunn et al. (2) that the failure to detect carbon dioxide by capnography can be misleading and must be combined with clinical evaluation in diagnosing the placement of the endotracheal tube. In two cases described by these authors, successful endotracheal intubation was indeed achieved though with some difficulty, but because of severe bronchospasm in the first case and equipment malfunction in the second, capnography failed to confirm correct positioning. In both instances the authors correctly chose to trust their clinical assessment, despite reports that clinical assessment is not always reliable, and that "end-tidal carbon dioxide measurement is at present perhaps the most reliable means under all circumstances of determining proper tube position" (3). We were disappointed, though, that the authors did not, for completeness, discuss the scenario of esophageal intubation where capnography demonstrates a false-positive waveform (4). We believe that this is a far more serious situation, for the very reasons discussed by Edelist (1), i.e., that clinical signs may be ignored in the face of conflicting monitoring data.

Previously described in several reports, the scenario of

detection of carbon dioxide inflated into the stomach during ventilation via mask can lead to the false security propagated by an initial, "quick" glimpse at the capnograph. Contrary to the assessment of Birmingham et al. (3) that the capnograph waveform will appear irregular and of low amplitude, others have noted that the initial waveform may be indistinguishable from that of endotracheal intubation (4-6).

The discussion by Dunn et al. is indeed enlightening, but the evaluation of technologies that tend to draw us further away from trusting our clinical skills need consider the false-positives as well as the false-negatives, lest we become even more secure with a positive test result. This becomes even more important for those of us in training programs, where our clinical skills are developed in the shadow of these technologies.

William H. Rosenblatt, MD
Department of Anesthesiology
Yale University School of Medicine
New Haven, Connecticut

Armenuhi Kharatian, MD
Hospital No. 3
Yerevan, Armenia

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Book Reviews

Perioperative Autologous Transfusion

Linda Stehling, ed. Arlington, Virginia: American Association of Blood Banks, 1991, 177 pp, \$30.00.

Autologous blood is the transfusion of choice for avoidance of disease transmission. Clerical error or bacterial contamination of harvested units can still occur with autologous donation. However, the blood is otherwise completely safe for the recipient. In the contemporary climate of the AIDS crisis, transfusion practices are being scrutinized and changed. Homologous blood utilization continues to grow as does total blood utilization. Autologous units represent an underutilized resource. Continuous physician education and awareness will serve to increase the utilization of autologous units. The monograph, *Perioperative Autologous Transfusion* edited by Linda Stehling provides a wealth of information transcribed from a national conference held in Arlington, Virginia, in May 1990.

As a series of lectures from multiple contributors, the book carries a relaxed style that makes it different from most texts. The individual styles of the chapters are quite variable. Highlights include the following:

An introductory chapter by Steven Gould, MD, discussing the need to transfuse, makes a number of appropriate points. First, there is no clear consensus on what level of hemoglobin/hematocrit patients must possess to trigger transfusion. Patients without significant cardiovascular disease can survive extremely low levels (3.5 g/dL). His points about the trigger to transfuse are well made and should be well understood by all physicians. Perhaps most interesting is Dr. Gould's discussion of the frustrations of day-to-day patient care and scheduling autologous blood donations. Clearly, he has identified early in this book the major problem with the growth of autologous usage. He also points out that a pro-active system combining strategies for blood conservation, salvage, and autologous donation is most effective. The use of a nurse coordinator has helped enormously in smoothing the logistical inadequacies at his institution. To generalize that approach to the national level will require a major commitment throughout the health industry.

The topic of administering an autologous program is further discussed by Linda Stehling, MD. Many pitfalls can be avoided by advance planning, devising protocols, and scheduling coverage of the needed services appropriately. The key is truly to spend time in planning.

Two discussions compare a hospital-based autologous program and a regional blood center program. Kenneth Williamson, MD, reviewed the Mayo Clinic experience and nicely summarizes the advantages and disadvantages in a table. Mark Popovsky, MD, reviewed the Northeast Regional Blood Center's experiences and notes its advantages. From the two chapters, there is a consensus of them being complimentary approaches rather than contrasting or competitive ones.

The impact of autologous programs on blood utilization has been extensively studied. Data from cardiac surgery and

orthopedic cases are reviewed by Thomas Lane, MD, and Joseph C. McCarthy, MD, respectively. Both authors make strong cases for the use of autologous blood in decreasing transfusion during these operations. The use of filtered blood rather than washed processed cells is controversial, including the potential for enhancing coagulopathies. Dr. Schukri F. Kuri discusses that controversy in detail in a separate chapter. At least for moderate blood loss cases, the use of washed cells is safe and does not directly cause a coagulopathy.

Other chapters of particular interest enumerate the financial and legal implications. Three separate discussion sections provide answers to some of the most commonly asked questions including how to staff call schedules for cell saver personnel, the use of blood substitutes, and bacterial contamination of cell-saved products.

As an example of the underutilization of these techniques, the participants agreed that if there was even a 10% chance of a patient requiring blood products, then use of multiple autologous techniques should be appropriate. In summary, *Perioperative Autologous Transfusion* does provide an up-to-date summary of the available data and controversies surrounding the use of autologous blood. It may help to increase the use of this underutilized technique to avoid homologous transfusion and is appropriate reading for all persons involved in perioperative care.

Bruce D. Spiess, MD
University of Washington School of Medicine
Seattle, Washington

Preanesthetic Assessment

Volume 8, No. 4 of *Anesthesia Clinics of North America*

Elizabeth A. M. Frost, ed. Philadelphia: W. B. Saunders, 1990, 256 pp, \$32.00 (single issue), \$69.00 (annual subscription for four issues).

Preanesthetic Assessment contains 16 chapters and is organized according to patient population (e.g., preanesthetic assessment of the pediatric patient or obstetric patient) and to system disease (e.g., preanesthetic assessment of the cardiac, drug abuse, neurosurgical patient). The majority of the authors are on the faculty of the anesthesia department of Albert Einstein College of Medicine in the Bronx, New York where the guest editor is professor of anesthesiology. This fact probably explains the uniformity of the material presented.

This reviewer feels that the most beneficial feature of this book is that it puts at the reader's disposal the chance to review the clinically relevant aspects of several disease processes along with the important aspects of anesthesia care in a condensed and a handy way. Also, the book helps the reader review some areas of medicine, which are a bit removed from the core of the anesthesia body of knowledge, e.g., nuclear angiography of the heart, evaluation of thyroid function, and blood tests for AIDS. This material

will help anesthesiologists to communicate more readily with colleagues from other disciplines of medicine.

Several chapters were particularly useful, including those on coagulopathy, oncology, and substance abuse. There are, though, some topics that the reviewer wishes were included in the book—e.g., the indications for performing coronary angiography on the cardiac patient for noncardiac surgery. A discussion on the pathophysiology of the different varieties of chronic pulmonary obstructive diseases, the role of major conduction vs general anesthesia, and the preanesthetic evaluation of the patient with multiple organ failure are often missing topics.

The question that poses itself strongly is: is this a necessary book? Is this information presented in standard anesthesia textbooks or in subspecialty anesthesia texts? Certainly, but this handbook offers ready availability, practicality, and relevance; features that make it very useful for busy practicing anesthesiologists, for surgeons, and for internists involved in the perioperative care of the surgical patient.

Morris E. Antebi, MD
Burdette Tomlin Memorial Hospital
Cape May Court House, New Jersey

Manual of Anesthesia and the Medically Compromised Patient

E. Y. Cheng and J. Kay, eds., Philadelphia: J. B. Lippincott, 1990, 680 pp, \$42.50.

Every anesthesiologist needs a medicine text as a reference. Either one chooses a publication devoted solely to the subspecialties of internal medicine or one selects a text that integrates medical knowledge with the principles of anesthetic practice. The popularity of the latter group most likely stems from the anesthesiologist's desire to understand the concurrent medical illness as well as relate it to special preoperative evaluation or intraoperative management. The growing number of choices available in this domain reflects the need for this type of information to be readily available for the planning of a safe anesthetic.

The *Manual of Anesthesia and the Medically Compromised Patient* can best be described as a paperback version of Stoelting, Dierdorf, and McCammon's *Anesthesia and Co-Existing Disease*. Both of these texts are written for similar audiences and approach the subject matter in the same fashion. Reasons why one may prefer this *Manual of Anesthesia* are several. First, it chooses to eliminate bulkiness by concentrating on "the more commonly encountered medical illnesses." Of course, congestive heart failure, hypertension, and diabetes are thoroughly covered, but so are the likes of hypothyroidism, the thalassemias, and scleroderma. Only the more esoteric diseases (which the reader never heard of anyway) are not discussed. Second, the outline format of this book works very well. It is a full-text discussion for a given topic arranged in an outline structure with headings and subheadings for the convenience of the reader. It is not simply the pared-down highlights of a given topic compressed into an outline format or tables where the true meaning is sometimes lost in favor of an economy of words and space. Third, the cost is not prohib-

itive, and it allows for a minimal outlay of funds especially when successive, more current editions are published.

As with most first editions, there is room for improvement. The table of contents is inconsistent. Some chapters list the topics contained within for easy reference and rapid accessibility, whereas other chapters are simply listed by their title (e.g., Renal Disease, Malignancies) with no mention of their content. Each subsection of the book is accompanied by a summary of the anesthetic considerations. This usually consists of several paragraphs of relevant information that may be skimmed in less than a minute by a hurried anesthesiologist. Although the intent was good, the outcome was such that the summaries are too short and prone to generalizations to be of genuine usefulness in planning an anesthetic. Lastly, each topic is accompanied by a Recommended Reading list. The only fault here is that the references are from years 1988 and prior. Future editions (and there definitely should be) will hopefully come to press more quickly and will not suffer from this drawback.

On the average, one may be more inclined to shy away from a paperback manual and purchase a major reference text, especially when both are available on the same subject matter. However, this manual is a good mix of medicine and anesthesia and should not at all be considered less thorough because of its smaller size.

David M. Guarnieri, MD
Jefferson Medical College
Philadelphia, Pennsylvania

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Beck DE, Welling DR, eds. *Patient Care in Colorectal Surgery*. Boston: Little, Brown & Company, 1991, 351 pp, \$42.50.

Casey KL, ed. *Pain and Central Nervous System Disease. The Central Pain Syndromes*. New York: Raven Press, 1991, 304 pp, \$92.00.

Clements FM, de Bruijn NP. *Transesophageal Echocardiography*. Boston: Little, Brown & Company, 1991, 163 pp, \$95.00.

Dal Santo G. *A Rational Basis for Anesthesiology*. Padua, Italy: Piccin Nuova Libreria, 1991, 933 pp, \$80.00.

Diaz JH, ed. *Perinatal Anesthesia and Critical Care*. Philadelphia: W.B. Saunders, 1991, 395 pp.

Hoyt JW, Tonnesen AS, Alben SI, eds. *Critical Care Practice*. Philadelphia: W.B. Saunders, 1991, 571 pp.

Kvetan V, Gallagher TJ, eds. *Critical Issues in Critical Care. Anesthesiology Clinics of North America, Volume 9, No. 2*. Philadelphia: W.B. Saunders, 1991, 255 pp, \$74.00 subscription for four issues or \$32.00 single issue.

Lebowitz PW, ed. *Recovery From Anesthesia*. International Anesthesia Clinics, Volume 29, No. 2. Boston: Little, Brown & Company, 1991, 121 pp, \$81.00 annual subscription for four issues or \$39.00 single issue.

Madsen JB, Gold GE, eds. *The Effects of Anaesthetics upon Cerebral Circulation and Metabolism*. New York: Springer-Verlag, 1991, 160 pp, \$49.00.

Newfield P, Cottrell JE, eds. *Neuroanesthesia: Handbook of Clinical and Physiologic Essentials*. 2nd ed. Boston: Little, Brown & Company, 1991, 458 pp, \$50.00.

Norton ML, Brown A, Brown D, eds. *Atlas of the Difficult Airway*. St. Louis: Mosby-Year Book, 1991, 225 pp.

Rippe JM, Alpert JS, Fink MP, eds. *Intensive Care Medicine*, 2nd ed. Boston: Little, Brown & Company, 1991, 2071 pp, \$155.00.

A Guide for Authors

Manuscripts should be sent to:

Ronald D. Miller, MD
Editor-in-Chief
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All papers are reviewed by three or more referees. Acceptance is based on significance, originality, and validity of the material presented. Only one copy of an article not accepted for publication will be returned to the author.

The submitted manuscript should be accompanied by a covering letter that includes a statement to the editor about all submissions and previous reports that might be regarded as prior or duplicate publication of the same, or very similar work. The title page and abstract of such material should be included with the submitted manuscript to help the editor decide how to deal with the matter.

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals," reprinted in *The New England Journal of Medicine* 1991;324:424-8.

No manuscripts describing investigations carried out in humans will be accepted for publication unless the text states that the study was approved by the authors' institutional human investigation committee and that written informed consent was obtained from all subjects or, in the case of minors, from parents. No manuscript describing investigations in animals will be accepted for publication unless the text states that the study was approved by the authors' institutional animal investigation committee.

Human subjects should not be identifiable. Do not use patients' names, initials, or hospital numbers.

Authors and their typists should use the checklist given below for preparation of manuscripts:

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- ☐ Original articles describe in 3000 words or less clinical or laboratory investigations.
- ☐ Clinical reports describe in 1000 words or less either new and instructive case reports or anesthetic techniques and equipment of demonstrable originality, usefulness, and safety.
- ☐ Technical communications are papers that deal with instrumentation and analytic techniques.
- ☐ Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material to aid in evaluating new concepts.
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- ☐ Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration.
- ☐ *Results*: Present the results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations; emphasize or summarize only important observations.
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- ☐ *Units of measurement*: Measurements of distance/length and weight must be expressed in metric units only. Clinical laboratory and hematologic data must be expressed in SI units with, if desired, present conventional metric units in parentheses.

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Examples:

1. *Standard journal articles* (List all the authors when six or less; when seven or more, list only the first three and add et al.)
Rigler ML, Drasner K, Krejcie TC, et al. Cauda equina syndrome after continuous spinal anesthesia. *Anesth Analg* 1991;72:275-81.
2. *Personal author(s) of books and monographs*
Eisen HN. Immunology: an introduction to molecular and cellular principles of the immune response. 5th ed. New York: Harper and Row, 1974.
3. *Chapter in a book*
Weinstein L, Swartz NM. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

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- ☐ Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use lower-case italicized letters in alphabetical order.
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Effects of Cardiopulmonary Bypass and Cardioplegia on Regional and Global Cardiac Actions of Halothane in Dogs

Donat R. Spahn, MD, L. Richard Smith, PhD, Wei-chih Hu, PhD, Robert L. McRae, and Bruce J. Leone, MD

Division of Cardiac Anesthesia, Department of Anesthesiology, The Heart Center at Duke University and Division of Biometry, Department of Community and Family Medicine, Duke University Medical Center, Durham, North Carolina

Cardiopulmonary bypass (CPB) with aortic cross-clamping represents a controlled period of global cardiac ischemia. We hypothesized that CPB (asanguineous prime), with aortic cross-clamping and repeated cardioplegia, alters myocardial function, which would be manifested as an exaggerated myocardial depression caused by halothane after CPB. In nine dogs anesthetized with fentanyl and midazolam, halothane dose-response curves (0.0%–2.0%) were compared before and after CPB. A reduced mean arterial blood pressure (46.4 ± 3.7 vs 85.8 ± 5.9 mm Hg), associated with a marked hemodilution (hematocrit, $19\% \pm 1\%$ vs $41\% \pm 2\%$), was observed

after CPB. Cardiac output and systolic shortening were not significantly different after versus before CPB during fentanyl-midazolam anesthesia. Normalized to fentanyl-midazolam hemodynamics, halothane dose-response curves before and after CPB were identical for all variables except cardiac output, where halothane caused a slight but statistically significantly more pronounced decrease after CPB compared with before CPB. The effect of halothane on left ventricular function, therefore, is relatively unaffected by CPB with cardioplegia.

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Cardiopulmonary bypass (CPB) with aortic cross-clamping induces a controlled period of global myocardial ischemia, the effects of which are mitigated by hypothermia and cardioplegia. In previous experimental studies using a variety of preparations, as well as clinical studies in patients undergoing coronary artery bypass graft surgery, significant myocardial dysfunction after CPB has been observed (1–3). Compromised left ventricular (LV) function after CPB might result from residual ischemia, a myocardial stunning effect of CPB with cardioplegia (4), a hibernating state of the myocardium (5), de novo ischemia developing in the early post-CPB period because of low coronary perfusion pressure, or microemboli in the coronary circulation. If residual myocardial dysfunction from CPB and

aortic cross-clamping is present despite using standard cardioplegic protection of the heart (2,6,7), one might expect the cardiovascular system to be particularly sensitive to the known cardiovascular depressive actions of volatile anesthetics. The knowledge of the cardiovascular depressive properties of volatile anesthetics specifically in the early post-CPB period is important because volatile anesthetics may be used for anesthesia maintenance in that particular period.

We hypothesized that an asanguineous, moderate hypothermic CPB technique with repeated cardioplegia during aortic cross-clamping in otherwise normal myocardium alters myocardial function and that this change in myocardial function results in an increased sensitivity of the myocardium to the cardiodepressive actions of halothane in the early post-CPB period. Halothane was used in the present study because the cardiovascular actions of halothane and in particular its interaction with evolving ischemic dysfunction are best known among the volatile anesthetics.

Methods

All animals used in these experiments received humane care in compliance with the "Principles of Laboratory Animal Care" formulated by the National

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Address correspondence to Dr. Leone, Department of Anesthesiology, Duke University Medical Center, P.O. Box 3094, Durham, NC 27710.

Society for Medical Research and the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH Publication No. 80-23, revised 1978).

In nine unpremedicated dogs, weighing 22–26 kg, anesthesia was induced with thiopental (15–25 mg/kg IV). The trachea was intubated, and the animals were ventilated with 100% oxygen to normocarbina at a rate of 10 breaths/min (Ohio V5 Airco, Ohmeda, Madison, Wis.). End-tidal carbon dioxide and halothane concentrations were continuously measured by infrared spectroscopy (Datex model 254; Puritan Bennett Corporation, Wilmington, Mass.). During the surgical preparation, anesthesia was maintained with 1.0%–1.5% halothane (end tidal). The animals were placed in the supine position and an intravenous cannula was introduced in the hindlimb through which a continuous infusion of 0.9% saline ($3\text{--}4\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$) was begun. A 7F pressure-transducer tipped catheter (Millar Instruments, Houston, Tex.) was inserted in the femoral artery and advanced to the thoracic aorta, 1 cm distal to the left subclavian artery, to obtain aortic pressure and arterial blood gas analyses.

The heart was exposed through a median sternotomy and suspended in a pericardial cradle. A 5F pressure-transducer tipped catheter was inserted into the left ventricle through a stab incision at the apex of the heart to measure left ventricular (LV) pressure. The fat pad was dissected free of the aortic root, an appropriately sized 5-MHz Doppler ultrasonic flow probe was placed around the aortic root, and aortic blood flow velocity was measured with a Doppler flowmeter (model 100-1000-05; Triton Technologies, San Diego, Calif.).

A pair of ultrasonic crystals (diameter, 1.5–2 mm) oriented in the short axis of the heart was placed in the apical region of the LV anterior wall, the area that has been shown to be most sensitive to the depressant actions of halothane (8). The regional myocardial contraction pattern was assessed by continuously measuring the segment length between the two sonomicrometer crystals, based on the measurement of ultrasonic transit time (Sonomicrometer model 120; Triton Technologies) (9,10).

Experimental Protocol

After sternotomy, halothane was discontinued and initial boluses of fentanyl ($5\text{ }\mu\text{g/kg}$; total initial bolus dose, $10\text{ }\mu\text{g/kg}$) and midazolam ($50\text{ }\mu\text{g/kg}$; total initial bolus dose, $100\text{ }\mu\text{g/kg}$) were given, followed by continuous infusions (fentanyl, $0.1\text{--}0.2\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$; midazolam, $1\text{--}2\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). The time interval between initial bolus administrations was 3 min. At least 60 min elapsed before any pre-CPB measure-

ments were recorded. During this period, no further boluses of fentanyl or midazolam were administered, and the fentanyl and midazolam infusion rates were constant. First measurements were made during fentanyl-midazolam anesthesia (halothane 0%); halothane then was readministered and general hemodynamic parameters as well as regional function data were recorded with increasing concentrations of 1.0%, 1.5%, and 2.0% end-tidal halothane (halothane dose-response curve), with the fentanyl and midazolam infusions continuing throughout the entire halothane dose-response curve. At each halothane level, at least 10–15 min were allowed to reach a steady state, which was confirmed by infrared spectroscopy. After the pre-CPB halothane dose-response curve was obtained, halothane was discontinued and anesthesia was maintained with constant fentanyl and midazolam infusions during CPB as well as in the post-CPB period.

After heparin administration (300 U/kg), CPB was instituted by draining the venous blood from the right atrium and returning the arterialized blood to the proximal left subclavian artery. The CPB circuit was primed with 1000 mL of crystalloid and 500 mL of Dextran 70. The flow rate was set at $1.7\text{ L}\cdot\text{min}^{-1}\cdot\text{m}^{-2}$ and mean arterial blood pressure was held constant at 55–65 mm Hg by means of phenylephrine or nitroprusside infusions as necessary. Repeated arterial blood gas analyses were performed, and arterial CO_2 tension was corrected to a range of 30–40 mm Hg, arterial O_2 tension to a range of 100–200 mm Hg, and pH to a range of 7.35–7.45, and base excess was kept above -5 mEq/L using the alpha stat blood gas management. After having stabilized the animal at a body temperature of $28^{\circ}\text{--}32^{\circ}\text{C}$, the aorta was cross-clamped and the heart was arrested by an initial dose (350 mL) of cold (4°C) cardioplegia solution ($\text{Na} = 120$, $\text{K} = 16$, $\text{Ca} = 2.4$, $\text{Mg} = 32$, $\text{Cl} = 160$, $\text{HCO}_3 = 20\text{ mEq/L}$, heparin = 1000 U/L , procainamide = 50 mg/L , osmolality = 300 mOsm/L , $\text{pH} = 7.80$ at 4°C), which was infused into the aortic root using a 14-gauge DLP aortic root cannula with vent (DLP, Inc., Grand Rapids, Mich.). The heart was packed in crushed ice and a septal myocardial temperature (Shiley, Irvine, Calif.) between 14° and 18°C resulted. After 20 min, a second dose of cardioplegia solution (250 mL) was infused. The aortic cross-clamp was released at 40 min and rewarming was started. At a stable body temperature of $36^{\circ} \pm 1^{\circ}\text{C}$, the animals were weaned from CPB (mean total CPB time, $157 \pm 10\text{ min}$) and the right atrium was decannulated. The animal was stabilized at an LV end-diastolic pressure of 5–8 mm Hg, and at $48 \pm 2\text{ min}$ after CPB (at least 30 min after the last administration of any inotropic agent or sodium bicarbonate), the post-CPB halothane dose-response curve was recorded (halothane

in addition to the continuous infusions of fentanyl and midazolam). No positive inotropes, CaCl_2 , or sodium bicarbonate were administered during recording of the post-CPB halothane dose-response curves.

Data Processing, Calculations, and Statistics

The pressure signals were amplified by a low-noise direct current preamplifier (Grass Instruments, Quincy, Mass.), digitally converted (analog-to-digital converter, model 16AF; MetraByte Corporation, Taunton, Mass.), and recorded with a personal computer (model 386; Compaq Computer Corporation, Houston, Tex.) at a sampling rate of 500 Hz over a period of 10 s.

Stroke volume was obtained as the product of the perfused cross-sectional area of the aortic flow probe and the systolic aortic blood flow velocity time integral, and cardiac output was computed as the product of stroke volume and heart rate. LV dP/dt , the first derivative of LV pressure, was determined as the instantaneous slope of the LV pressure-time curve using a five-point differentiation. End-diastole was defined by the first consistent positive deflection of LV dP/dt and end-systole by the abrupt cessation of forward blood flow in the aortic root, indicating aortic valve closure.

Derived cardiovascular parameters were computed according to standard formulas. Systemic vascular resistance (SVR) [$\text{dyne}\cdot\text{s}\cdot\text{cm}^{-5}$] was computed as

$$\text{SVR} = \text{MAP} \times 80/\text{CO},$$

where MAP = mean arterial pressure (mm Hg) and CO = cardiac output (L/min) (1), and coronary perfusion pressure was computed as diastolic aortic pressure minus LV end-diastolic pressure (LVEDP). Blood viscosity was calculated from the measured hematocrit (Hct) based on the data of Rand et al. (11); an exponential curve was fit to the viscosity data, from 0% to 60% hematocrit, determined at a shear rate of 212 s^{-1} and 37°C (12). The exponential regression analysis yielded

$$\eta = e^{0.3612 + 0.0251 \text{ Hct}}, \quad r^2 = 0.9966,$$

where η = viscosity (cp). Vascular resistance (VR) ($\text{dyne}\cdot\text{s}\cdot\text{cm}^{-5}\cdot\text{cp}^{-1}$) was then calculated as $\text{VR} = \text{SVR}/\eta$ (12).

The end-diastolic segment length and end-systolic length were determined using the above definitions for end-diastole and end-systole. Systolic shortening (SS) and post-systolic shortening (PSS) were calculated as

$$\text{SS} = [(\text{EDL} - L_{\text{minS}})/\text{EDL}] \times 100 \quad (\text{Reference 10}),$$

$$\text{PSS} = [(L_{\text{minS}} - L_{\text{minD}})/(\text{EDL} - L_{\text{minD}})] \times 100 \quad (\text{Reference 13}),$$

where EDL = end-diastolic segment length, L_{minS} = minimum length obtained during systole, and L_{minD} = minimum length obtained during early diastole. For subsequent statistical analyses, negative values for PSS were listed as zero (14).

The effect of halothane on hemodynamic variables and the effects of CPB on halothane dose-response curves were statistically examined by means of a multifactorial analysis of variance with a complete block design using the general linear model procedure in SAS (version 6.04; SAS Institute, Cary, N.C.). Three main effects and one interaction were estimated. The main effects were (a) dog, which was used to remove dog-to-dog variability, (b) halothane dose, and (c) time (before vs after CPB). In addition, the halothane dose-time interaction was estimated as an overall test for whether the response of an individual variable was different before versus after CPB. Values measured during fentanyl-midazolam anesthesia before and after CPB were compared by least-squares means estimation using general linear model. Measured values as well as values normalized to pre- and post-CPB fentanyl-midazolam were analyzed. Because three dogs died during recording of the post-CPB halothane dose-response curve (one at 1.5% and two at 2.0% end-tidal halothane), two different analyses were performed: one with all available data ($n = 9$, Table 1) and a second including only data of the six dogs with a complete post-CPB halothane dose-response curve. Because the results were similar in both analyses, numbers in text and figures (mean \pm SEM) are based on all available data, and they represent raw means. Pre- and post-CPB hematocrit and viscosity values were compared by paired t -tests. The significance level was considered to be 0.05, and 0.01 was considered to be highly significant.

Results

Halothane dose-response curves before cardiopulmonary bypass. Before CPB, halothane induced the expected significant dose-dependent decreases in cardiac output (Figure 1), MAP (Figure 2), coronary perfusion pressure, heart rate, maximum positive LV dP/dt (LV $\text{dP/dt}_{\text{max}}$) (Table 1), SS (Figure 3), SVR (Figure 4), and vascular resistance (Table 1). Left ventricular end-diastolic pressure, end-diastolic segment length, stroke volume, and PSS did not change with increasing halothane concentrations (Table 1).

Fentanyl-midazolam hemodynamics before versus after cardiopulmonary bypass. Because of the asanguineous CPB prime, hematocrit ($19\% \pm 1\%$) and the calculated

Table 1. Hemodynamic Effects of Increasing Halothane Concentration Before Versus After Cardiopulmonary Bypass During Fentanyl-Midazolam Anesthesia*

Halothane (%)	Before CPB				After CPB			
	0 (n = 9)	1.0 (n = 9)	1.5 (n = 9)	2.0 (n = 9)	0 (n = 9)	1.0 (n = 9)	1.5 (n = 8)	2.0 (n = 6)
HR (beats/min)	133 ± 7	119 ± 6	106 ± 3	96 ± 3 ^b	127 ± 8	110 ± 10	109 ± 6	99 ± 13 ^b
LVEDP (mm Hg)	8.3 ± 1.3	6.8 ± 1.0	5.4 ± 1.0	5.6 ± 1.2	7.8 ± 2.7	5.9 ± 1.0	6.7 ± 1.3	6.1 ± 1.1
CPP								
(mm Hg)	66.1 ± 5.6	43.6 ± 4.1	32.2 ± 4.5	22.0 ± 2.6 ^b	26.9 ± 3.0 ^c	16.3 ± 2.6	12.4 ± 2.7	12.8 ± 2.5 ^{b,d}
(% FM)		66.0 ± 3.3	49.4 ± 6.5	34.3 ± 4.2 ^b		60.2 ± 9.0	43.9 ± 8.8	43.3 ± 6.7 ^b
VR								
(dyne·s·cm ⁻⁵ ·cp ⁻¹)	596 ± 108	458 ± 66	392 ± 46	343 ± 20 ^b	654 ± 107	639 ± 149	744 ± 231	727 ± 243 ^d
(% FM)		81.0 ± 4.9	72.0 ± 5.5	67.1 ± 6.9 ^b		96.7 ± 10.9	110.6 ± 13.0	117.0 ± 15.9 ^d
SV								
(mL)	25.3 ± 3.0	23.9 ± 2.6	22.6 ± 2.9	21.6 ± 3.2	24.0 ± 4.1	21.0 ± 3.7	17.7 ± 3.6	16.9 ± 7.7
(% FM)		97.7 ± 6.8	92.1 ± 7.9	88.2 ± 9.5 ^b		86.7 ± 8.4	65.3 ± 8.9	66.2 ± 8.8 ^{b,d}
LV dP/dt _{max}								
(mm Hg·s ⁻¹)	1627 ± 191	978 ± 113	646 ± 86	440 ± 51 ^b	1262 ± 197 ^c	630 ± 95	474 ± 67	456 ± 112 ^b
(% FM)		64.1 ± 3.7	42.2 ± 5.4	29.0 ± 3.7 ^b		49.8 ± 5.7	36.5 ± 4.0	33.0 ± 3.8 ^b
EDL (mm)	10.9 ± 1.0	10.6 ± 0.9	10.6 ± 0.8	10.9 ± 0.9	10.4 ± 1.0	10.7 ± 0.9	11.3 ± 1.1	10.7 ± 1.3
PSS (%)	1.2 ± 1.1	3.4 ± 2.3	3.1 ± 3.1	6.4 ± 4.6	4.8 ± 3.3	7.4 ± 3.6	11.4 ± 6.3	12.5 ± 7.3

CPB, cardiopulmonary bypass; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; CPP, coronary perfusion pressure; VR, vascular resistance; SV, stroke volume; LV dP/dt_{max}, maximum LV dP/dt; EDL, end-diastolic length; PSS, postsystolic shortening.

*Absolute values as well as values normalized to pre- and post-cardiopulmonary bypass fentanyl-midazolam (%). Values are mean ± SEM.

^bSignificant ($P < 0.01$) effect of increasing halothane concentrations.

^cSignificant ($P < 0.01$) difference versus pre-cardiopulmonary bypass FM.

^dSignificant difference ($P < 0.01$) between pre- and post-cardiopulmonary bypass halothane dose-response curves.

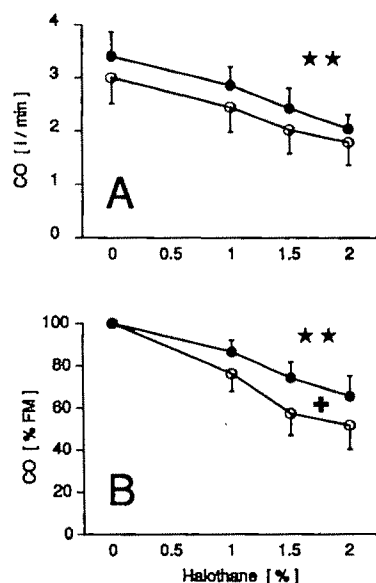


Figure 1. Cardiac output (CO) before (●) and after (○) cardiopulmonary bypass. (A) Measured values (L/min). (B) Values normalized to pre- and post-cardiopulmonary bypass fentanyl-midazolam (FM) (% FM). ★★, Significant ($P < 0.01$) effect of increasing halothane concentrations; +, significant difference ($P < 0.05$) between pre- and post-cardiopulmonary bypass halothane dose-response curves.

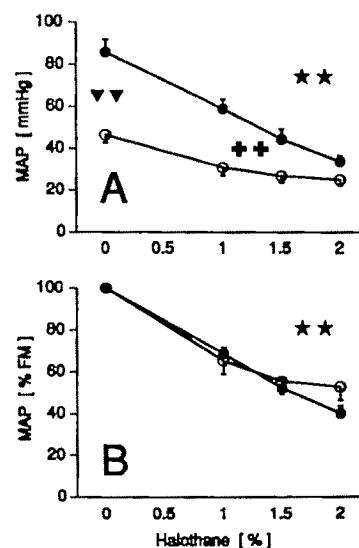


Figure 2. Mean arterial pressure (MAP) before (●) and after (○) cardiopulmonary bypass. (A) Measured values (mm Hg). (B) Values normalized to pre- and post-cardiopulmonary bypass fentanyl-midazolam (FM) (% FM). ★★, Significant ($P < 0.01$) effect of increasing halothane concentrations; ▼▼, significant ($P < 0.01$) difference versus before cardiopulmonary bypass FM; ++, significant difference ($P < 0.01$) between pre- and post-cardiopulmonary bypass halothane dose-response curves.

blood viscosity (2.33 ± 0.07 cp) were significantly lower after CPB ($p < 0.01$) than before CPB ($41\% \pm 2\%$; 4.06 ± 0.17 cp). The most striking difference

between fentanyl-midazolam hemodynamics after versus before CPB was the considerably lower MAP (Figure 2, Table 1). Cardiac output (Figure 1), SS

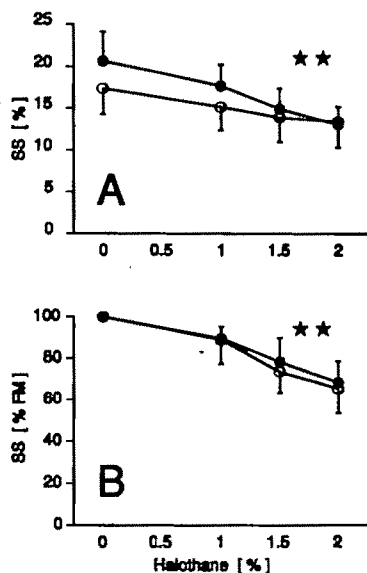


Figure 3. Systolic shortening (SS) before (●) and after (○) cardiopulmonary bypass. (A) Measured values (%). (B) Values normalized to pre- and post-cardiopulmonary bypass fentanyl-midazolam (FM) (% FM). ★★, Significant ($P < 0.01$) effect of increasing halothane concentrations.

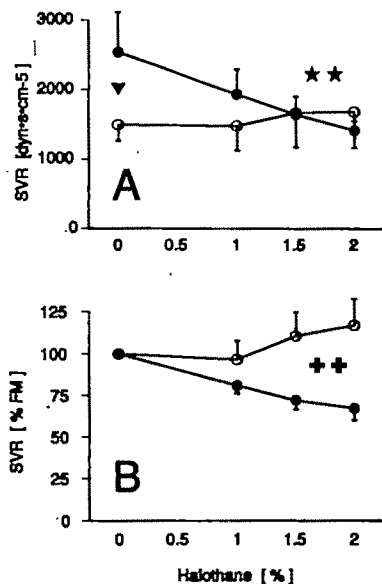


Figure 4. Systemic vascular resistance (SVR) before (●) and after (○) cardiopulmonary bypass. (A) Measured values (dyne·s·cm⁻⁵). (B) Values normalized to pre- and post-cardiopulmonary bypass fentanyl-midazolam (FM) (% FM). ★★, Significant ($P < 0.01$) pre-cardiopulmonary bypass effect of increasing halothane concentrations; ▼, significant ($P < 0.05$) difference versus pre-cardiopulmonary bypass FM; ++, significant difference ($P < 0.01$) between pre- and post-cardiopulmonary bypass halothane dose-response curves.

(Figure 3), PSS, stroke volume, VR, heart rate, LVEDP, and end-diastolic segment length remained unchanged (Table 1). Systemic vascular resistance

(Figure 4), coronary perfusion pressure, and LV dp/dt_{max} were decreased significantly after versus before CPB (Table 1).

Halothane dose-response curves before versus after cardiopulmonary bypass. Normalized to fentanyl-midazolam hemodynamics (halothane 0%), the changes in MAP (Figure 2), heart rate, LVEDP, LV dp/dt_{max} , end-diastolic segment length, and SS induced by halothane (Figure 3) were identical before and after CPB (Table 1). The relative decrease in cardiac output (Figure 1) was slight, but statistically significantly more pronounced after CPB with increasing halothane concentrations as compared with the pre-CPB observations. The changes in SVR (Figure 4) and VR differed significantly before versus after CPB: before CPB these resistance indices decreased at increasing halothane concentrations; after CPB, SVR (Figure 4) and VR were unchanged over the entire range of halothane concentrations investigated. Averaged over the entire halothane dose-response curves, PSS was significantly higher ($P < 0.05$) after CPB as compared with before CPB. However, the post-CPB changes in PSS with increasing halothane concentrations were statistically not different from PSS changes during recording of pre-CPB halothane dose-response curves.

Discussion

The most important finding of the present study is that halothane dose-response curves before and after CPB were nearly identical with regard to LV function. The hypothesis, therefore, that asanguineous CPB with cardioplegia alters regional and global LV function and sensitivity of the myocardium to the cardio-depressive actions of halothane is not substantiated in the present study.

The pre-CPB halothane effects on cardiovascular function are influenced by the background continuous infusions of fentanyl and midazolam, and thus direct comparisons with previous studies are fraught with difficulty. Decreases in MAP (Figure 2), coronary perfusion pressure, LV dp/dt_{max} , and cardiac output (Figure 1) are in keeping with previous reports of the effects of halothane in different experimental models (13,15-17). The reported heart rate effects at increasing halothane concentrations are variable; no change (16,17), a decrease (13), and an increase in heart rate with halothane (15) have all been reported. An interaction with opioids might be suspected, as the dogs showing an increase in heart rate were not premedicated (15); the animals showing a constant or decreasing heart rate had received premedication of 0.3-1.5 mg/kg of morphine sulfate (13,16,17). Systemic vascular resistance has been reported to be

unchanged by halothane (15,17). In contrast to these studies, SVR (Figure 4) decreased before CPB in the present study, which may represent an interaction between halothane and fentanyl-midazolam. Constant LVEDP at increasing halothane concentrations has been observed (13); however, a small increase in LVEDP has also been reported with increasing halothane concentrations (15-17). Systolic shortening of the LV anterior wall at 2.0% end-tidal halothane is depressed by 24%-46% (13,16,17); the depression of SS during recording of the pre-CPB halothane dose-response curve in the present study (Figure 3) was similar to that observed in these previous reports. A halothane-fentanyl-midazolam interaction therefore seems to be less important in terms of local LV anterior wall contractility. Moderate PSS at 2.0% inspired halothane concentration has also been reported (13). Thus the pre-CPB halothane-induced changes in global cardiovascular and regional myocardial function observed in this study are in keeping with those changes previously reported.

The most striking finding in post-CPB global hemodynamics as compared with pre-CPB hemodynamics was the very low MAP; the post-CPB hematocrit and calculated viscosity were also markedly reduced. In the present study, blood viscosity was calculated based on data reported by Rand et al. (11). Although their viscosity values fit perfectly to an exponential regression model, this approach may only yield an estimate of the true viscosity of blood because the influence of fibrinogen on blood viscosity was not taken into account (18). However, according to the law of Laplace, viscosity is part of the total resistance in any fluid-dynamic system (12), and therefore the low post-CPB blood viscosity as compared with the pre-CPB blood viscosity may explain the low SVR and arterial pressures observed in this study after CPB.

Three animals did not survive the post-CPB halothane dose-response protocol. The (incomplete) post-CPB halothane dose-response curves of these three nonsurviving animals, however, compared with their respective (partial) pre-CPB halothane dose-response curves in a way similar to that of the (complete) post-CPB halothane dose-response curves with respect to the (complete) pre-CPB halothane dose-response curves in surviving animals. Thus, the three nonsurviving animals did not show an exaggerated susceptibility to halothane after CPB. The reason why these animals did not survive the recording of the post-CPB halothane dose-response curves remains speculative; of interest, these three animals were also the three most severely hemodiluted animals after CPB and had lower values for mean arterial and coronary perfusion pressures as compared with the six animals that completed the post-CPB halo-

thane protocol. Thus, these animals started their post-CPB halothane dose-response curves with relatively low mean arterial and coronary perfusion pressures and probably could not stand any further pressure decrease because of increasing concentrations of halothane, notably pressure decreases similar to the pressure decreases in their pre-CPB halothane dose-response curves. The fact that these three animals died during the post-CPB protocol, therefore, is not in contradistinction to the basic finding of this study, i.e., the LV depressive action of halothane is relatively unaffected by CPB and cardioplegia.

Left ventricular function with fentanyl-midazolam was well preserved after CPB as compared with before CPB, evidenced by the lack of a significant change in cardiac output (Figure 1) or SS (Figure 3). The LV myocardium therefore was neither stunned nor in a hibernating state after CPB; both states are characterized by an impaired myocardial function. In addition, no ischemic regional dysfunction, such as a depressed SS or the appearance of significant PSS (13,16,17), was observed. Alternately, LV dp/dt_{max} was significantly reduced after versus before CPB (Table 1), which may be taken as evidence for a reduced LV contractility (19), as preload (LVEDP, end-diastolic segment length) and heart rate were not significantly different before and after CPB (Table 1). A slightly decreased global LV contractility after CPB with repeated cold cardioplegia would agree with previous reports from a canine LV bypass model, showing reduced levels of high-energy phosphates and reduced LV peak pressure development after CPB and aortic cross-clamping with standard high-potassium cardioplegia (2). The reduced value for LV dp/dt_{max} might represent an isolated finding of minor physiologic significance, or one might speculate that a considerably reduced LV afterloading after CPB, as evidenced by a lower SVR with fentanyl-midazolam after CPB (Figure 4), enabled the heart to maintain cardiac output and SS of the LV anterior free wall at pre-CPB levels despite a reduced LV contractility. In addition to a decreased LV dp/dt_{max} , PSS (averaged over the entire halothane dose-response curve) was found to be higher after CPB than it was before CPB, which suggests some increased myocardial dysfunction after CPB. The absence of exaggerated depression of SS in the post-CPB halothane dose-response curve and of a marked increase in PSS during post-CPB fentanyl-midazolam anesthesia, however, would suggest that little, if any, ischemic damage was present (16). Despite the fact that there were small differences in LV dp/dt_{max} as well as in PSS, no physiologically significant depression of LV function, therefore, resulted from asanguineous CPB with cardioplegia in the present study.

The only differences in post- versus pre-CPB halo-

thane dose-response curves were a slight but statistically significantly more pronounced decrease in cardiac output (Figure 1) and stroke volume and an altered reaction of SVR to increasing halothane concentrations. Whereas before CPB, SVR and vascular resistance decreased, these resistance indices remained constant after CPB (Figure 4), which may represent a homeostatic mechanism to preserve MAP. The slightly more pronounced decrease in cardiac output (Figure 1) and stroke volume after versus before CPB with increasing halothane concentrations may indicate reduced cardiac reserves, may be the result of a very low coronary perfusion pressure during recording of the post-CPB halothane dose-response curves (Table 1), or may indicate an increased susceptibility for the depressive action of halothane after CPB. Without a correspondingly steeper decrease in SS and LV dp/dt_{max} during recording of post-CPB halothane dose-response curves, indicating exaggerated halothane-induced LV depression, an increased LV susceptibility for the depressive action of halothane after CPB seems unlikely. Right ventricular function, however, may become the limiting factor in overall cardiac performance, in particular with low coronary perfusion pressures (14). Thus impairment of right ventricular function may have caused the observed slight, but statistically significantly more pronounced, decrease in cardiac output after CPB. This decrease in post-CPB cardiac output induced by halothane therefore may occur without a corresponding decrease in regional or global LV contractility. Within the limits of the present study, however, this remains speculative.

Halothane improves recovery of regional function after a transient ischemic episode (20). In the study of Warltier et al. (20), halothane was administered during a 15-min total coronary occlusion and thus affected the development of stunned myocardium. In the present study, halothane was administered only before and after CPB, and no important myocardial dysfunction was evident after CPB.

Because halothane is known to cause myocardial depression (13,15-17), changes in hemodynamic measures were expected in this study. We therefore chose to analyze, in particular, the difference between relative changes in myocardial function and global hemodynamics induced by halothane after versus before CPB to better characterize the effects of asanguineous CPB with cardioplegia on the cardiovascular effects of halothane. We did not analyze individual differences in raw data between halothane levels, but rather performed a separate, independent comparison between the 0% halothane (fentanyl-midazolam) data before and after CPB. Thus, our analysis specifically examined the data to detect an exaggerated dose response to halothane after CPB.

The effect of CPB in absolute terms is illustrated by comparing the pre- and post-CPB fentanyl-midazolam 0% halothane results.

In conclusion, the effects of asanguineous moderate hypothermic CPB with repeated cardioplegia on the cardiovascular actions of halothane have been investigated in the present study. Pre- and post-CPB halothane dose-response curves were found to be identical for most of the investigated cardiovascular variables. Only cardiac output and stroke volume showed slightly more pronounced post- versus pre-CPB decreases at increasing halothane concentrations, and SVR reacted differently before and after CPB. Left ventricular cardiodepressive actions of halothane, therefore, are relatively unaffected by CPB with cardioplegia in a normal heart.

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Comparison of Nalbuphine and Fentanyl Anesthesia for Coronary Artery Bypass Surgery

Hemodynamics, Hormonal Response, and Postoperative Respiratory Depression

Branko M. Weiss, MD, Edith R. Schmid, MD, and Ruth I. Gattiker, MD

Institute of Anesthesiology, Division of Cardiovascular Anesthesia, University Hospital Zurich, Zurich, Switzerland

To determine whether nalbuphine might replace fentanyl as the principal opioid for anesthesia during coronary artery bypass surgery, 20 patients undergoing myocardial revascularization were anesthetized with flunitrazepam and with a continuous infusion of either nalbuphine (an opioid agonist-antagonist) or fentanyl (a pure opioid agonist) in equipotent dosage ratio of 333:1. During endotracheal intubation, all patients given nalbuphine, but only one given fentanyl ($P < 0.05$), required nitroglycerin to control arterial blood pressure. Two minutes after tracheal intubation, plasma values of epinephrine, norepinephrine, vasopressin, and cortisol did not change in the fentanyl group compared with the awake (baseline) levels, whereas catecholamines and vasopressin significantly increased with nalbuphine compared with the baseline and with the values in the fentanyl group. A steady state of anesthesia (30 min after intubation), when compared with the baseline, was characterized by unchanged systemic and pulmonary blood pressures and increased systemic vascular resistance with nalbuphine, by decreased systemic and pulmonary pressures and resistances with fentanyl, and by comparably decreased cardiac index with both opioids. Hormone values returned to baseline levels but norepinephrine remained significantly higher in

the nalbuphine than in the fentanyl group. A bolus injection of either nalbuphine (2.5 mg/kg) or fentanyl (7.5 μ g/kg) given during the steady-state period of anesthesia provoked only minimal hemodynamic changes. Before skin incision, 7 of 10 patients receiving nalbuphine required nitroglycerin to control arterial blood pressure. After sternotomy, both groups required nitroglycerin, but additional antihypertensive drugs were necessary mainly in the nalbuphine group. All hormone concentrations significantly increased in patients given nalbuphine, as compared with the baseline and anesthesia steady-state levels; whereas they did not exceed the baseline values in the fentanyl group before cardiopulmonary bypass. The median time periods required for tracheal extubation were 169 and 555 min ($P < 0.05$) after nalbuphine (average intraoperative dose, 18.9 ± 3.1 mg/kg) and fentanyl (51.7 ± 10.0 μ g/kg), respectively. Postoperatively, 5 of 10 patients given nalbuphine complained of recall, pain, or unpleasant dreams during or after the procedure. Despite the advantage of early tracheal extubation, the authors conclude that flunitrazepam-nalbuphine cannot be recommended for anesthesia in patients undergoing coronary artery surgery.

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Nalbuphine was introduced into clinical practice as an opioid agonist-antagonist with sedative and analgesic properties and a ceiling effect for respiratory depression (1-4). Although its use in patients with coronary or valvular heart disease was associated with stable hemodynamic func-

tion, nalbuphine alone produces inadequate surgical anesthesia (5). The analgesic activity of nalbuphine and its potency as an anesthetic supplement has, however, been said to be limited (4,6-10) and self-reversed with high doses (11,12). On the other hand, nalbuphine may be a valuable adjunct to inhaled anesthetics (13) by maintaining hemodynamic stability during cardiac surgical procedures (14), prolonging postoperative analgesia (10,13,14), and enabling early tracheal extubation (13,14).

The purpose of the present study was to determine whether nalbuphine, combined with a potent benzodiazepine, might replace fentanyl as the principal opioid used for anesthesia during coronary artery

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Address correspondence to Dr. Weiss, Institute of Anesthesiology, University Hospital Zurich, CH-8091 Zurich, Switzerland.

bypass surgery. The possibility that the ceiling effect for respiratory depression might result in a shorter period of postoperative controlled ventilation and earlier tracheal extubation was particularly intriguing. The dosage ratio of nalbuphine to fentanyl of 333:1, when administered by continuous infusion, was extrapolated from the ratio of morphine to nalbuphine of 1:1 (2-4) and from the highest morphine-to-fentanyl dosage ratio previously reported (15,16) and then verified in three pilot cases. Flunitrazepam, in a dose larger than that previously used in combination with fentanyl for anesthesia in patients having myocardial revascularization (17,18), was chosen to assure smooth anesthetic induction, adequate sedation, and reliable amnesia for the procedure with both opioids. No inhaled anesthetics were used. The study thus enabled the comparison of nalbuphine and fentanyl with regard to their effects on hemodynamic function and hormonal responses during the procedure and on analgesia and respiratory depression after the procedure.

Methods

After institutional approval was obtained, 20 patients scheduled for coronary artery bypass surgery were prospectively randomized to receive either nalbuphine or fentanyl. Informed consent was obtained from each patient during the preoperative visit. Patients with stenosis of the left main coronary artery, myocardial infarction within 3 mo before surgery, or valvular heart disease were not included in the study. Usual preoperative medications and 2 mg of oral flunitrazepam were given in the morning, 2-3 h and 30-90 min, respectively, before instrumentation.

After arrival of the patient in the operating room, leads II and V₅ electrocardiogram electrodes were attached. Peripheral venous, radial arterial, and pulmonary arterial (VIP 93A-831, Edwards) catheters as well as a separate central venous catheter (for opioid infusion only) were introduced under local anesthesia. Electrocardiogram and all pressures were monitored continuously on an oscilloscope and recorded on a multichannel recorder. Hemodynamic measurements included heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, central venous pressure, and cardiac output. Cardiac output was measured by thermodilution (9520-A, Edwards), by injection of 10 mL of ice-cool saline solution into the central venous port randomly distributed within the respiratory cycle, and calculated as the mean of three to five determinations. Analyses of arterial blood gases (940, AVL), mixed venous oxygen saturation, and hemoglobin concentration (OSM2, Radiometer) accompanied each hemodynamic measurement. He-

moglobin binding capacity was taken as 1.34 mL O₂/g hemoglobin. Cardiac index (CI), systemic (SVR) and pulmonary vascular resistances, and oxygen delivery and consumption indices were calculated using standard formulas. Blood for the hormonal assays, drawn initially from a peripheral vein and later from the pulmonary artery, was immediately transferred in an ice-bath to the reference laboratory. Plasma levels of epinephrine and norepinephrine were determined by a radioenzymatic method (19) with a sensitivity of 15 pg/mL for both catecholamines. Vasopressin and cortisol levels were measured by radioimmunoassay commercial kits with a sensitivity of 0.9 pmol/L (Buehlman) and 50 nmol/L (New England Nuclear), respectively.

After blood withdrawal in the awake patients for baseline measurements of plasma hormone levels, infusion of 7 mL/kg of lactated Ringer's solution, and measurement of baseline hemodynamic function, anesthesia was started with a continuous infusion of either opioid delivered by a calibrated infusion pump (Table 1). Manual ventilation via a mask (Fio₂, 1.0) replaced spontaneous breathing as soon as verbal commands were no longer responded to and/or respiratory rate decreased. After 10-15 min of opioid infusion, flunitrazepam (20 µg/kg) and pancuronium (100 µg/kg) were given intravenously and the trachea was intubated after topical anesthesia of the upper airways. Mean arterial blood pressure increases of more than 20% above baseline levels were treated with an intravenous nitroglycerin bolus of 100-200 µg. Controlled ventilation (900B, Siemens) was instituted at a rate of 12 strokes/min using an Fio₂ of 0.5 in air and zero end-expiratory pressure. End-expiratory CO₂ was adjusted to 4.5-5.5 vol% and arterial CO₂ tension was kept at 4.5-5.5 kPa (kPa × 7.502 = mm Hg) throughout the procedure. Blood samples for hormonal assays were taken 2 min after tracheal intubation. At that time the rate of opioid infusion was halved. An anesthesia steady state was assumed to be present 30 min after intubation, when hemodynamic and hormonal measurements were repeated. Thereafter a bolus of nalbuphine (2.5 mg/kg) or fentanyl (7.5 µg/kg) was rapidly administered intravenously, followed by measurements of the hemodynamic function after a delay of 1, 5, and 10 min. Before skin incision, the opioid infusion rate was increased to the induction rate and 7.5 µg/kg of flunitrazepam was given. Increases in MAP after skin incision were treated with nitroglycerin and, if necessary, with additional antihypertensive drugs. Hemodynamic and hormonal measurements were repeated 2 min and, if cardiopulmonary bypass (CPB) was not yet instituted, 30 min after sternotomy. At that time the opioid infusion was again halved and stopped on initiation of CPB. At the beginning of

Table 1. Study Protocol

	Nalbuphine (mg·kg ⁻¹ ·min ⁻¹)	Fentanyl (μg·kg ⁻¹ ·min ⁻¹)	
Baseline			Hemodynamics Hormones
Induction	0.1	0.3	
Intubation + 2 min			Hormones
	0.05	0.15	
Intubation + 30 min (Anesthesia steady state)			Hemodynamics Hormones
Bolus injection + 1, 5, 10 min	2.5 mg/kg →	← 7.5 μg/kg	
	0.1	0.3	Hemodynamics
Sternotomy + 2 min			Hemodynamics Hormones
	0.05	0.15	
Sternotomy + 30 min			Hemodynamics Hormones
Cardiopulmonary bypass			
Rewarming	0.025	0.075	
End of procedure			Hemodynamics Hormones

Each patient received 35 μg/kg of intravenous flunitrazepam i.e., 7.5 μg/kg for instrumentation, 20 μg/kg for induction, and 7.5 μg/kg before skin incision.

rewarming the opioid infusion was restarted at one-fourth of the induction rate. All measurements were repeated after closure of the sternum; the opioid infusion was stopped at the end of the surgical procedure. Postoperatively, no sedatives were given. Pain was controlled with nicomorphine (0.5 mg/10 kg) upon request by the patient. Nitroglycerin (continuous infusion) was used to keep MAP less than 90 mm Hg, with other antihypertensive drugs added as necessary. As soon as the core temperature reached 36°C, attempts to wean the patients from the ventilator were initiated. Cooperation of the patient, adequate spontaneous ventilation, stable hemodynamics, and absence of significant blood loss were the criteria for extubation of the trachea. All patients were interviewed 24 h after extubation and asked to assess the quality of anesthesia and postoperative analgesia.

Results were summarized separately for each group and expressed as the mean ± standard deviation (SD). Because of the asymmetric distribution of the individual values of hormone plasma concentrations, nitroglycerin and nicomorphine requirements, and postoperative time periods, the median (25th–75th percentile) values have been considered more appropriate to express them correctly. Comparison of data between the two groups and within each group was analyzed by paired comparison with the Wilcoxon rank two-sample test and the Wilcoxon rank one-sample test, respectively. Fisher's exact probability test was applied to analyze the difference

between the number of patients within each group and between the two groups. Statistical significance was defined at $P < 0.05$.

Results

Patients' characteristics and the intraoperative time-course were comparable in both groups (Table 2). The

Table 2. Patients' Characteristics and Intraoperative Time-Course

	Nalbuphine	Fentanyl
Females/males	2/8	2/8
Age (yr) ^a	57.1 ± 6.9	52.7 ± 7.4
Weight (kg) ^a	70.2 ± 8.1	70.0 ± 10.4
Surface area (m ²) ^a	1.79 ± 0.1	1.78 ± 0.16
Ejection fraction (%) ^a	61 ± 12	61 ± 10
Previous myocardial infarction	8	5
History of arterial hypertension	5	5
Preoperative medication	9	10
β-Blocking agents	8	8
Calcium-channel antagonists	7	9
Nitrates	8	8
Time periods (min) ^a		
Induction-intubation	18 ± 2	17 ± 1
Induction-anesthesia steady state	55 ± 9	56 ± 9
Cardiopulmonary bypass	94 ± 41	87 ± 35
Operation	220 ± 72	195 ± 37
Anesthesia	351 ± 67	337 ± 54
Coronary anastomoses ^a	4 ± 2	4 ± 1

^a Mean ± SD.

baseline hemodynamic variables summarized in Table 3 were not different between the two groups except for a smaller cardiac index in the patients randomized to receive fentanyl.

The continuous infusion of either opioid produced sedation in all patients. In one patient given nalbuphine, heart rate decreased from 48 to 30 beats/min and then stabilized at a rate of 38–44 beats/min without intervention. After flunitrazepam and pancuronium administration and ventilation via a mask, a stable anesthetic state was achieved in all patients. During and after tracheal intubation, however, all patients given nalbuphine (and one patient given fentanyl) required nitroglycerin to control MAP (Table 4). During the steady state of anesthesia, systemic and pulmonary pressures as well as CI were significantly below baseline levels in patients anesthetized with fentanyl (at the cumulative dose of $11.8 \pm 1.8 \mu\text{g/kg}$), whereas in those anesthetized with nalbuphine ($4.5 \pm 0.9 \text{ mg/kg}$) pulmonary capillary wedge pressure and CI decreased as well, but systemic and pulmonary pressures remained unchanged, so that the calculated resistances increased slightly but significantly (Table 3). Calculated as percentage changes (Figure 1), CI during anesthesia steady state decreased below and pulmonary vascular resistance increased above baseline values with both opioids. Thus, the lower systemic and pulmonary artery pressures with fentanyl (and no change with nalbuphine), and the small but significant change in SVR in the opposite direction, dominated the hemodynamic differences between the two opioids during steady state of anesthesia. A bolus injection of $7.5 \mu\text{g/kg}$ of fentanyl and 2.5 mg/kg of nalbuphine, respectively, within anesthesia steady state produced only minimal additional hemodynamic changes after 1, 5, and 10 min: SVR decreased by 8%–10% with fentanyl and remained either unchanged or increased by 6% with nalbuphine (Table 3, Figure 1). However, in five patients of the nalbuphine group who had a preoperative history of arterial hypertension, SVR was significantly higher ($P < 0.05$) during the steady state of anesthesia ($1727 \pm 125 \text{ dyne}\cdot\text{s}\cdot\text{cm}^{-5}$) and 10 min after bolus injection ($1906 \pm 163 \text{ dyne}\cdot\text{s}\cdot\text{cm}^{-5}$) as compared with the SVR of another five patients without a history of hypertension (1556 ± 82 and $1578 \pm 76 \text{ dyne}\cdot\text{s}\cdot\text{cm}^{-5}$, respectively). After completion of the presurgical hemodynamic measurements, seven of ten patients given nalbuphine required nitroglycerin to control MAP before skin incision (Table 4).

After sternotomy (at a cumulative dose of $13.1 \pm 2.2 \text{ mg/kg}$ of nalbuphine or $39.5 \pm 8.5 \mu\text{g/kg}$ of fentanyl), nitroglycerin was necessary in both groups. Additional drugs to control HR and MAP were required more frequently in the nalbuphine

than in the fentanyl group (Table 4). Within the fentanyl group, patients with a preoperative history of arterial hypertension required significantly more nitroglycerin in the pre-CPB period than patients without a history of hypertension ($2500 [550\text{--}3175]$ vs $0 [0\text{--}675] \mu\text{g}$, $P < 0.05$). No such influence could be noticed in the nalbuphine group. Two and thirty minutes after sternotomy, MAP was kept near baseline levels in all but one patient in the nalbuphine group, in whom an increase in MAP up to 110 mm Hg was accompanied with a tachycardia of 120 beats/min and transient ST segment depression. Compared with the values during anesthesia steady state, HR, CI, and oxygen delivery and consumption significantly increased in the nalbuphine group, accompanied by decreased vascular resistances. The same comparison revealed that in the fentanyl group the hemodynamic function was characterized by increased vascular resistances and unchanged HR, CI, and oxygen delivery and consumption (Table 3, Figure 1). All patients were weaned from CPB without pacemaker stimulation or inotropic support. After CPB, nitroglycerin requirements did not differ between the two groups (Table 4). At the end of the procedure, at the time when filling pressures were comparable, CI was maintained in both groups by HR (negative ratio of stroke volume index to HR) and not by stroke volume as was found before and during the procedure (Figure 1).

Plasma levels of epinephrine, norepinephrine, vasopressin, and cortisol (Figures 2–5) remained within baseline values after tracheal intubation and sternotomy in the fentanyl group, whereas they increased after tracheal intubation and significantly exceeded the baseline levels after sternotomy in the nalbuphine group. At the end of the procedure, however, plasma catecholamines, vasopressin, and cortisol levels were significantly higher than the baseline and anesthesia steady-state levels in both groups. Vasopressin plasma concentrations (Figure 4) were not different between the two groups, but higher epinephrine (Figure 2) and cortisol (Figure 5) levels with nalbuphine than with fentanyl were seen at the end of surgery. There was no difference throughout the procedure in the hormonal responses between the patients with and without a history of arterial hypertension. At the end of the surgical procedure, norepinephrine plasma levels (Figure 3) were significantly higher ($P < 0.05$) in patients with than in those without a history of arterial hypertension with both opioids (nalbuphine: $2226 [2162\text{--}2289]$ vs $1103 [1056\text{--}1150] \text{ pg/mL}$; fentanyl: $840 [700\text{--}983]$ vs $550 [546\text{--}564] \text{ pg/mL}$, respectively).

The total intraoperative dose of nalbuphine averaged $18.9 \pm 3.1 \text{ mg/kg}$, that of fentanyl $51.7 \pm 10.0 \mu\text{g/kg}$, and that of flunitrazepam $35 \mu\text{g/kg}$.

Table 3. Hemodynamic Data in the Nalbuphine and Fentanyl Groups

	Group	Baseline	Anesthesia steady state	Bolus injection			Sternotomy		End of procedure
				1 min	5 min	10 min	2 min	30 min	
HR (beats/min)	N	64 ± 10	64 ± 12	63 ± 13	61 ± 11	61 ± 12	74 ± 20	71 ± 20	94 ± 9 ^c
MAP (mm Hg)	F	56 ± 8	53 ± 9 ^a	52 ± 9 ^{a,c}	52 ± 8	51 ± 8 ^c	54 ± 10 ^a	52 ± 8 ^a	74 ± 9 ^{a,c}
	N	90 ± 13	82 ± 12	87 ± 17	84 ± 14	89 ± 12	85 ± 14	91 ± 16	86 ± 15
MPAP (mm Hg)	F	89 ± 10	64 ± 8 ^{a,b}	63 ± 9 ^a	63 ± 10 ^a	64 ± 9 ^a	85 ± 18 ^c	82 ± 16 ^c	72 ± 9 ^{a,c}
MPAP (mm Hg)	N	15 ± 5	14 ± 4	15 ± 4	15 ± 5	15 ± 4	14 ± 4	15 ± 4	14 ± 2
PCWP (mm Hg)	F	16 ± 3	11 ± 3 ^b	11 ± 2 ^a	11 ± 2 ^a	12 ± 3	12 ± 3	11 ± 2	15 ± 3 ^c
PCWP (mm Hg)	N	9 ± 3	7 ± 3 ^b	10 ± 3	9 ± 3	8 ± 4	8 ± 2	8 ± 3	8 ± 2
CVP (mm Hg)	F	10 ± 3	6 ± 3 ^b	6 ± 3 ^a	5 ± 2 ^a	6 ± 3	6 ± 2	6 ± 2	9 ± 2
CVP (mm Hg)	N	5 ± 3	5 ± 2	6 ± 2	5 ± 2	5 ± 3	4 ± 3	5 ± 4	6 ± 3
CI (L·min ⁻¹ ·m ⁻²)	F	6 ± 2	4 ± 2 ^b	5 ± 3 ^c	4 ± 2	5 ± 2 ^c	5 ± 3	3 ± 3	7 ± 3 ^c
	N	2.61 ± 0.31	2.12 ± 0.36 ^b	2.27 ± 0.54	2.24 ± 0.38	2.19 ± 0.33	2.92 ± 0.71 ^c	2.99 ± 0.9	2.46 ± 0.62
SVR (dynes·cm ⁻⁵)	F	2.32 ± 0.29 ^a	1.78 ± 0.20 ^{a,b}	1.89 ± 0.15 ^c	1.92 ± 0.20 ^a	1.93 ± 0.18 ^c	1.77 ± 0.33 ^a	1.68 ± 0.26 ^a	2.28 ± 0.66 ^c
	N	1508 ± 183	1635 ± 144 ^b	1636 ± 276	1624 ± 234	1742 ± 210	1304 ± 453 ^c	1339 ± 399	1546 ± 474
PVR (dynes·cm ⁻⁵)	F	1642 ± 337	1516 ± 231	1381 ± 167 ^{a,c}	1343 ± 197 ^{a,c}	1381 ± 223 ^{a,c}	2109 ± 478 ^{a,c}	2198 ± 369 ^{a,c}	1373 ± 311
PVR (dynes·cm ⁻⁵)	N	99 ± 50	131 ± 46 ^b	117 ± 61	126 ± 58	127 ± 59	91 ± 43	102 ± 35	117 ± 66
DO ₂ I (mL·min ⁻¹ ·m ⁻²)	F	105 ± 61	136 ± 48	136 ± 40	126 ± 35	128 ± 41	163 ± 40 ^a	151 ± 34	113 ± 29
DO ₂ I (mL·min ⁻¹ ·m ⁻²)	N	433 ± 65	368 ± 72 ^b	388 ± 100	377 ± 59	371 ± 61	510 ± 156 ^c	531 ± 159	346 ± 125
VO ₂ I (mL·min ⁻¹ ·m ⁻²)	F	399 ± 72	316 ± 49 ^b	328 ± 44	329 ± 50	332 ± 46 ^c	308 ± 70 ^a	292 ± 75 ^a	320 ± 96
VO ₂ I (mL·min ⁻¹ ·m ⁻²)	N	102 ± 21	88 ± 11 ^b	92 ± 19	90 ± 11	86 ± 12	101 ± 29	116 ± 24 ^c	123 ± 20 ^c
VO ₂ I (mL·min ⁻¹ ·m ⁻²)	F	97 ± 14	82 ± 11 ^b	82 ± 14	83 ± 14	85 ± 10	82 ± 15	83 ± 17 ^a	104 ± 32 ^c

HR, heart rate; MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CVP, central venous pressure; CI, cardiac index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; DO₂I, oxygen delivery index; VO₂I, oxygen consumption index; N, nalbuphine; F, fentanyl.

Data are mean ± SD.

^aP < 0.05, nalbuphine vs fentanyl.

^bP < 0.05, vs baseline.

^cP < 0.05, vs anesthesia steady state.

Table 4. Antihypertensive Drug Interventions

	Nalbuphine	Fentanyl
Nitroglycerin		
Total (μg) ^a	4425 (1563-8438)	938 ^b (125-3238)
Between skin incision and CPB (μg)	2550 (856-4389)	550 (0-2625)
No. of patients/periods		
Intubation	10	1 ^b
Before skin incision	7	0 ^b
Between skin incision and CPB	10	7
After CPB	9	8
Additional drugs ^c		
No. of patients	8	2 ^b

CPB, cardiopulmonary bypass.

^aMedian (25th-75th).

^b $P < 0.05$.

^cBetween skin incision and CPB: phenolamine (fentanyl group); phenolamine combined with verapamil, propranolol, or clonidine (nalbuphine group).

Postoperatively (Table 5), nine of ten patients anesthetized with nalbuphine could be tracheally extubated within 4 h or less. The time required for

EPINEPHRINE, pg/ml

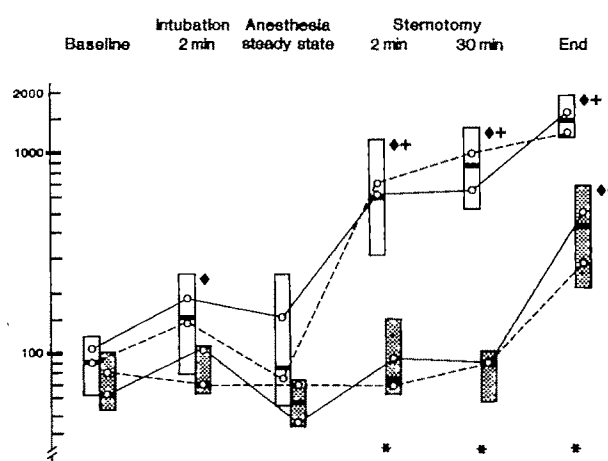


Figure 2. Plasma concentrations of epinephrine in the nalbuphine (open bar) and fentanyl (stippled bar) group (box plots: median, 25th-75th). * $P < 0.05$, nalbuphine vs fentanyl. ♦ $P < 0.05$, vs baseline. + $P < 0.05$, vs anesthesia steady state. Solid lines, median values in patients with preoperative history of arterial hypertension within each group; broken lines, median values in patients without preoperative history of arterial hypertension within each group.

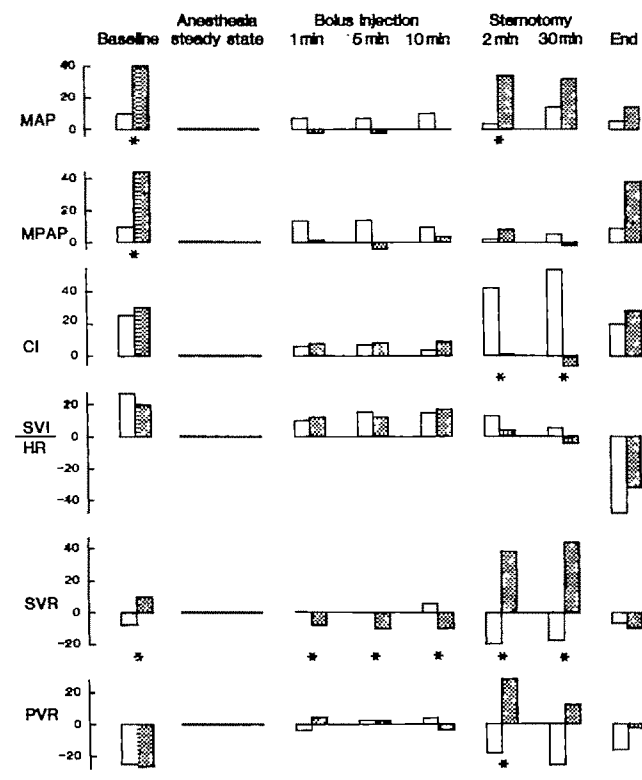


Figure 1. Mean percent hemodynamic changes compared with anesthesia steady state (= 0%) in the nalbuphine (open bar) and fentanyl (stippled bar) groups. MAP, mean arterial pressure; MPAP, mean pulmonary artery pressure; CI, cardiac index; SVI/HR, stroke volume index/heart rate ratio; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance. * $P < 0.05$, nalbuphine vs fentanyl.

respirator weaning and tracheal extubation was significantly longer in the fentanyl than in the nalbuphine group. The cumulative nicomorphine dose required within the first 12 h was not different between the two groups. One patient who received nalbuphine became very restless immediately upon entering the intensive care unit and required 40 mg of intravenous nicomorphine to control pain during the first 2 h. The patients in the nalbuphine group required more antihypertensive drugs to control MAP postoperatively than those in the fentanyl group.

When interviewed 24 h after tracheal extubation, all patients in the fentanyl and five of ten patients in the nalbuphine group reported complete satisfaction and that they had been amnesic for the whole procedure. Three patients given nalbuphine had been awake and experienced painful events during the surgical procedure before CPB; one of them admitted to be accustomed to regular alcohol consumption. Another patient complained of unpleasant and painful dreams after the procedure. The patient given nalbuphine, who was restless immediately after the operation, showed an increase of creatine-kinase (CK) plasma levels, from 153 U/L preoperatively to 3567 U/L postoperatively. The plasma levels of myocardial CK (CK-MB) and serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase increased from 9, 17, and 10 U/L to 96, 105, and 17 U/L, respectively. The enzyme levels peaked on the second postoperative day (CK, 6108;

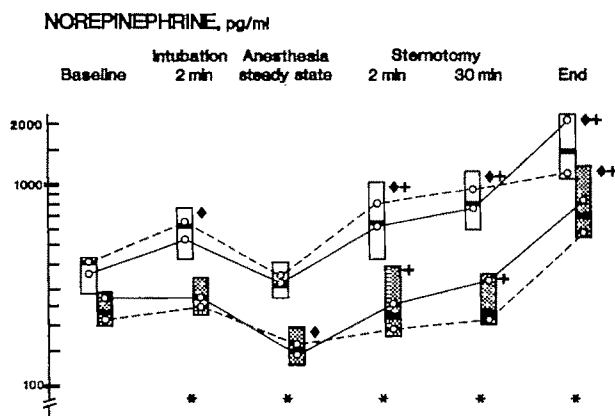


Figure 3. Plasma concentrations of norepinephrine in the nalbuphine (open bars) and fentanyl (stippled bars) group (box plots: median, 25th–75th). * $P < 0.05$, nalbuphine vs fentanyl. ♦ $P < 0.05$, vs baseline. * $P < 0.05$, vs anesthesia steady state. Solid lines, median values in patients with preoperative history of arterial hypertension within each group; broken lines, median values in patients without preoperative history of arterial hypertension within each group.

CK-MB, 312; serum glutamic oxaloacetic transaminase, 221), accompanied by a mild myoglobinemia (5.6 nmol/L; normal, 0–3.7). All values returned to normal on the fifth day. All patients studied recovered uneventfully, without electrocardiographic and enzymatic evidence of myocardial infarction, and were discharged from the hospital without delay.

Discussion

In this study of two similar groups of patients undergoing myocardial revascularization, nalbuphine, compared with fentanyl anesthesia in the equipotent dosage ratio of 333:1 and combined with flunitrazepam, showed insufficient potency to control cardiovascular and hormonal responses to endotracheal intubation and surgical stimulation. The period of postoperative controlled ventilation was significantly shorter in patients receiving nalbuphine than in those given fentanyl. However, five of ten patients were not satisfied by nalbuphine anesthesia after the procedure.

The dose-response relationship of the opioid agonist-antagonist nalbuphine and pure opioid agonists is considered to be nonlinear and to disappear with increasing doses (3,4,7–9,11,12). Lower doses of nalbuphine and fentanyl, in a wide and arbitrary ratio of 60–239:1 (8,10,20), as well as higher doses of nalbuphine (14), comparable to our study, have been previously studied and more or less successfully combined with inhaled anesthetics and other drugs. In our study, nalbuphine and fentanyl infusions were supplemented with flunitrazepam, a benzodiazepine

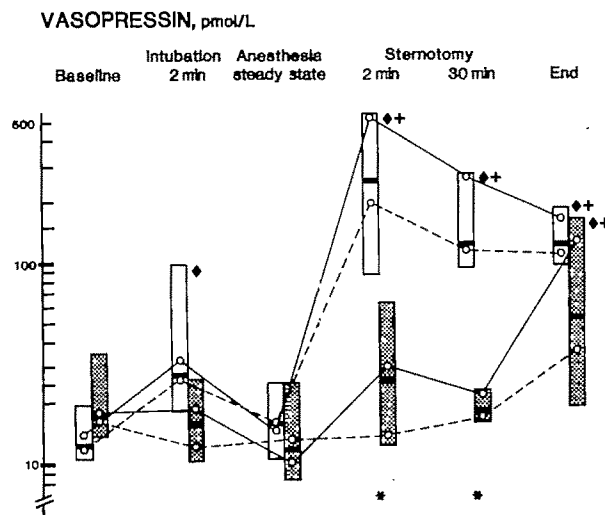


Figure 4. Plasma concentrations of vasopressin in the nalbuphine (open bar) and fentanyl (stippled bar) group (box plots: median, 25th–75th). * $P < 0.05$, nalbuphine vs fentanyl. ♦ $P < 0.05$, vs baseline. * $P < 0.05$, vs anesthesia steady state. Solid lines, median values in patients with preoperative history of arterial hypertension within each group; broken lines, median values in patients without preoperative history of arterial hypertension within each group.

with potent sedative and vasodilating properties (17,18). As supplements to opioid anesthesia, the benzodiazepines contribute to the sedation and hemodynamic and hormonal stability of patients undergoing coronary artery bypass surgery (14,16–18,21–29). Given in equal doses to all of our patients, flunitrazepam, in contrast to its combination with fentanyl, failed to improve the potency of nalbuphine. So, higher doses of flunitrazepam or the addition of an inhaled anesthetic, as previously reported (10,13,14,20), might have been required to improve the potency of nalbuphine in our patients. On the other hand, even higher doses of nalbuphine, as we believe, would not improve the potency or overall assessment of flunitrazepam-nalbuphine anesthesia. With increasing dose of nalbuphine, given as a continuous infusion for postoperative pain release, an analgesic ceiling effect has been previously described. A further dose increase then led to a predominating antagonist property that reversed the analgesic effect of nalbuphine (11,12).

Nalbuphine failed to suppress the increase of MAP (nitroglycerin required in all patients) and hormonal response to tracheal intubation. The hemodynamic function was characterized during anesthesia steady state by a comparable and slight decrease of filling pressures and a comparable decrease of CI with fentanyl (30%) and nalbuphine (25%) as compared with the baseline levels. However, in contrast to the additive effect of benzodiazepine and fentanyl (16–18,21,26), nalbuphine counteracted the vasodilation,

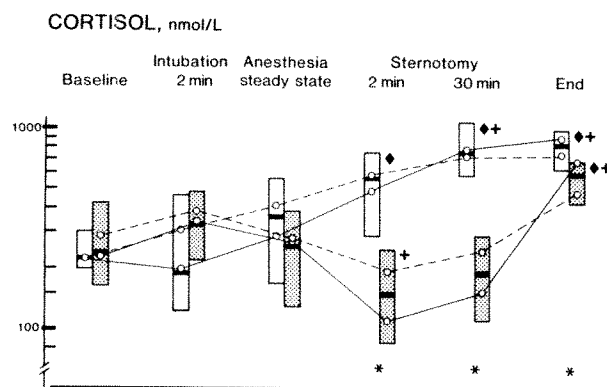


Figure 5. Plasma concentrations of cortisol in the nalbuphine (open bar) and fentanyl (stippled bar) group (box plots: median, 25th–75th). * $P < 0.05$, nalbuphine vs fentanyl. ++ $P < 0.05$, vs baseline. + $P < 0.05$, vs anesthesia steady state. Solid lines, median values in patients with preoperative history of arterial hypertension within each group; broken lines, median values in patients without preoperative history of arterial hypertension within each group.

maintaining unchanged arterial and pulmonary artery blood pressures. The rapid bolus injection of each opioid during the steady state of anesthesia produced minimal hemodynamic effect only within the first 5 min in our patients. Increased SVR 10 min after bolus injection of nalbuphine in patients with a preoperative history of arterial hypertension and nitroglycerin requirements before skin incision in most patients given nalbuphine may indicate the slight but significant potential of the opioid agonist-antagonist nalbuphine to provoke circulatory stimulation.

Despite normal MAP in all patients preoperatively, five patients with a history of arterial hypertension who were given fentanyl required significantly larger amounts of antihypertensive drugs than the five other patients in the fentanyl group. In patients receiving nalbuphine, antihypertensive drug requirements were larger than in the fentanyl group and were not influenced by the history of preoperative hypertension.

Table 5. Postoperative Period

	Nalbuphine	Fentanyl
Spontaneous ventilation (min) ^a	127 (88–202)	515 ^b (435–807)
Extubation (min) ^a	169 (154–250)	555 ^b (480–896)
Nicomorphine (mg/12 h) ^a	16.0 (8.8–28.3)	6.5 (0–16.5)
No. of patients		
Shivering	2	6
Requiring nitroglycerin	9	8
Requiring nifedipine	4	4
Requiring additional drugs	7	1 ^b

^aMedian (25th–75th).

^b $P < 0.05$.

The hormonal responses during anesthesia before incision and after sternotomy were clearly dependent on the choice of the opioid and not influenced by the history of hypertension. In our patients, flunitrazepam-fentanyl, similar to other potent anesthetic techniques (14,16,22,23,25,29) and in contrast to flunitrazepam-nalbuphine, suppressed the catecholamines, vasopressin, and cortisol increases after sternotomy. However, we cannot exclude that nitroglycerin (30), phentolamine (31), or other antihypertensive drugs might have contributed to the hormonal differences between the two groups in the pre-CPB period. On the other side, hormonal reactions during and after CPB (16,22–25) smoothed the difference between nalbuphine and fentanyl anesthesia at the end of the procedure.

In the postoperative period, the time required for tracheal extubation in our patients receiving fentanyl-flunitrazepam (10 h) is comparable to the extubation time after several other anesthetic techniques used in patients for coronary artery bypass surgery (14,16,24,25,27,28). The combination of nalbuphine and flunitrazepam, however, enabled very early tracheal extubation in our patients (less than 3 h) but did not provide adequate postoperative analgesia. The postoperative restlessness in one nalbuphine-treated patient was probably provoked by sudden awakening with intense pain, as a high nicomorphine dose calmed the patient and assured sufficient amnesia 24 h later. The short-lasting muscular activity eventually induced enzymatic release and mild myoglobinemia, which returned to normal several days later.

In conclusion, as previously pointed out (4–9) and reconfirmed by our study, the complex pharmacodynamics make nalbuphine unreliable in supplementing surgical anesthesia. Nalbuphine lacks the property to attenuate cardiovascular and hormonal responses to anesthetic and particularly surgical procedures. The advantage of very early postoperative extubation was negated by the poor subjective assessment in half of our patients. Based on this study, flunitrazepam-nalbuphine cannot be recommended for anesthesia for patients undergoing coronary artery bypass operations.

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Oxygen Uptake and Mixed Venous Oxygen Saturation During Aortic Surgery and the First Three Postoperative Hours

Jean P. Viale, MD, Guy J. Annat, MD, François M. Ravat, MD, Christian M. Pommier, MD, Jean R. Brudon, MD, Claude J. Desuzinges, MD, Olivier M. Bertrand, PhD, and Jean P. Motin, MD

Département d'Anesthésie-Réanimation, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France

This study was designed to determine the significance of changes in mixed venous oxygen saturation ($S\bar{V}O_2$) associated with aortic surgery. In 12 patients undergoing aortic aneurysm repair, $S\bar{V}O_2$ was monitored using a fiberoptic pulmonary arterial catheter, and oxygen uptake ($\dot{V}O_2$) was measured at 2-min intervals by a mass-spectrometer system. Excluding the phase of aortic clamping, $\dot{V}O_2$, hemoglobin, and arterial oxygen saturation were moderately stable during anesthesia, and changes in $S\bar{V}O_2$ were correlated with changes in cardiac output (CO). $S\bar{V}O_2$ remained stable during infrarenal aortic clamping, but increased during supraceliac aortic clamping.

During the first three postoperative hours, changes in $S\bar{V}O_2$ were opposite to changes in $\dot{V}O_2$ and CO. They were especially marked in the patients whose preoperative left ventricular ejection fraction was less than 50%. We conclude that $S\bar{V}O_2$ changes are an indicator of same-direction changes in CO during general anesthesia except during periods of aortic clamping. The interpretation of $S\bar{V}O_2$ changes is more complex during aortic clamping and during the immediate postoperative period, two critical periods during which simultaneous changes in $\dot{V}O_2$ and CO occur.

(Anesth Analg 1991;73:530-5)

The recent development of reliable fiberoptic reflectance oximetry systems allows continuous monitoring of mixed venous oxygen saturation ($S\bar{V}O_2$) in critically ill patients (1). However, the clinical usefulness of $S\bar{V}O_2$ remains unclear. The main concern with $S\bar{V}O_2$ is that its value is related to four physiologic variables: directly to hemoglobin concentration, cardiac output (CO), and arterial blood oxygen saturation (SpO_2), and inversely to whole body oxygen consumption ($\dot{V}O_2$). Therefore, in the usual clinical setting, changes in $S\bar{V}O_2$ prompt the assessment of each of these four variables.

When monitoring $S\bar{V}O_2$ during abdominal aortic surgery, three periods of time are of special interest. The first is maintenance anesthesia excluding aortic cross-clamping. $\dot{V}O_2$, SpO_2 , and hemoglobin concentrations probably remain within a narrow range; therefore, changes in $S\bar{V}O_2$ should be mainly due to changes in CO. The second period of interest is that

of cross-clamping of the aorta, which may affect the value of $S\bar{V}O_2$ owing to changes in CO, organ perfusion, and oxygen consumption. The third period of interest is the immediate postoperative period during which an increase in oxygen demand occurs.

In this study, we measured $S\bar{V}O_2$ and the four variables it depends on ($\dot{V}O_2$, CO, SpO_2 , and hemoglobin) in the course of abdominal aortic surgery. Our main objectives were: (a) to evaluate the relationship between $S\bar{V}O_2$ and CO during the period of general anesthesia excluding aortic cross-clamping, (b) to examine $S\bar{V}O_2$ changes associated with aortic cross-clamping at two levels (infrarenal aortic clamping and supraceliac aortic clamping), and (c) to examine, in the immediate postoperative period, the evolution of $S\bar{V}O_2$, $\dot{V}O_2$, and CO in patients who differed by their myocardial status assessed preoperatively by dipyridamol thallium and technetium pyrophosphate imaging.

Methods

Approval by the ethics committee of our institution and informed consent were obtained to study 12

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Address correspondence to Dr. Viale, Service de Réanimation, Pavillon G, Hôpital Edouard Herriot, Place d'Arsonval 69437, Lyon Cédex 03, France.

patients scheduled for abdominal aortic aneurysm repair. The aortic cross-clamping was applied infra-renally in six patients and proximally to the celiac artery in the others. In patients 2 and 4, treatment of a renal artery stenosis was associated with abdominal aortic aneurysm. Within 7 days before surgery, each patient underwent dipyrindamole thallium imaging, according to a previously described method (2). Left ventricular ejection fraction was measured by technetium pyrophosphate imaging. The limit between normal and abnormal ejection fraction was arbitrarily defined as the value of 50%.

Preanesthetic medication consisted of oral hydroxyzine (1.5 mg/kg body wt). Anesthesia was induced with intravenous etomidate (0.3 mg/kg), fentanyl (5 μ g/kg), and atracurium (0.5 mg/kg). After tracheal intubation, anesthesia was maintained with nitrous oxide, 0.5%–0.6% end-tidal isoflurane, and continuous infusion of fentanyl (7–8 μ g·kg⁻¹·h⁻¹). During the same time, atracurium was continuously infused (0.5 mg·kg⁻¹·h⁻¹) and the lungs of patients were mechanically ventilated. Arterial blood pressure was maintained within 20% of the preoperative value and pulmonary capillary wedge pressure between 10 and 15 mm Hg. This was achieved by administration of fluids intravenously (blood or colloid) when arterial blood pressure decreased or by the injection of fentanyl (2 μ g/kg) when arterial blood pressure increased. During aortic cross-clamping this goal was achieved by increasing end-tidal isoflurane. In the two patients having supraceliac cross-clamping, nitroprusside was used. An autotransfusion system (Cell Saver 4; Haemonetics, Braintree, Mass.) was used to reduce the number of blood products required.

During the first three postoperative hours, the patients received the same care including administration of a single dose of morphine (100 μ g/kg subcutaneously at the beginning of the recovery period), continuous monitoring, and mechanical ventilation on the assist-control mode. The occurrence of shivering was assessed every 5 min as the presence of muscular fasciculation in the masseter muscle or continuous or violent tremor. After this 3-h period, the patients were transferred to the Intensive Care Unit for continuation of, or weaning from, artificial ventilation.

Oxygen consumption was measured at 2-min intervals during the following periods: (a) the 20 min preceding anesthesia, using a face mask and a Laerdal valve for separation of inspired and expired flow, (b) the anesthetic period, and (c) the first three postoperative hours. SpO_2 and $\text{S}\bar{\text{V}}\text{O}_2$ were continuously monitored during the same periods. Cardiac output was measured every 15 min throughout the study time. In addition, measurements of CO were

performed whenever a therapeutic intervention was required to maintain arterial blood pressure within normal limits. Hemoglobin was assessed serially, and arterial blood lactate concentrations were determined 2 min before and after declamping, at the end of surgery, and finally 90 and 180 min later.

Pulse oximetry was used to measure SpO_2 . Core temperature, $\text{S}\bar{\text{V}}\text{O}_2$ averaged over 2-min periods, and CO were measured by a fiberoptic pulmonary arterial catheter (Oxymetrix, Abbott) inserted under local anesthetic infiltration before induction of anesthesia. The catheter was calibrated using a reflective standard provided by the manufacturer. The accuracy of the system was assessed after insertion by comparing the $\text{S}\bar{\text{V}}\text{O}_2$ value of a mixed venous sample (Instrumentation Laboratory Cooximeter) and the value was displayed by the Oxymetrix system 1 min before sampling. The system was recalibrated if necessary. No further recalibration was done during the study time. End-expiration measurements of CO were made in triplicate and were averaged using injections of 10 mL of 5% dextrose in water. Oxygen consumption was measured using a mass spectrometer system designed to take into account the presence of anesthetic gases (3,4). As the body nitrogen stores after step changes in the fraction of inspired nitrogen (FIN_2) were in an unsteady state, the gas exchange data acquired during the 15 min after induction of anesthesia and after the withdrawal of nitrous oxide were discarded from analysis (5,6). Arterial blood lactate concentrations were determined by a spectrophotometric method (7).

All data are expressed as mean \pm SE. Metabolic and hemodynamic variables were analyzed by analysis of variance (Statgraphics SGS) for repeated measurements with Duncan's multiple-range follow-up tests (8). Correlations between CO and the $\text{S}\bar{\text{V}}\text{O}_2$ value observed immediately before each CO measurement were investigated by regression analysis using a regression formula that takes into account the physiologic relationship between CO and $\text{S}\bar{\text{V}}\text{O}_2$: $1/y = a + bx$, where y is CO and x is $\text{S}\bar{\text{V}}\text{O}_2$. Calculated correlation coefficients were averaged after Fisher Z transformation (9).

During the postoperative period, the relationship between changes in $\text{S}\bar{\text{V}}\text{O}_2$ and in $\dot{\text{V}}\text{O}_2$ were analyzed. This was done by calculating $\text{S}\bar{\text{V}}\text{O}_2$ percent change from normal according to the following formula:

$$\frac{|\text{S}\bar{\text{V}}\text{O}_2 \text{ peak} - \text{S}\bar{\text{V}}\text{O}_2 \text{ init}|}{|(\dot{\text{V}}\text{O}_2 \text{ peak} - \dot{\text{V}}\text{O}_2 \text{ init})/\dot{\text{V}}\text{O}_2 \text{ init}|}$$

where the $\text{S}\bar{\text{V}}\text{O}_2$ peak was the $\text{S}\bar{\text{V}}\text{O}_2$ value coinciding with the maximal $\dot{\text{V}}\text{O}_2$ value ($\dot{\text{V}}\text{O}_2$ peak) measured during the postoperative period, and $\text{S}\bar{\text{V}}\text{O}_2$ init and $\dot{\text{V}}\text{O}_2$ init were values measured at the beginning of

Table 1. Characteristics of Patients and Results of Preoperative Dipyridamole-Thallium and Technetium-Pyrophosphate Imaging

Patient No.	Age (yr)	Left ventricular ejection fraction (%)	Number of segments with initial defect	Number of segments with redistribution
Supraceliac aortic cross-clamping				
1	60	56	0	0
2	62	44	1	0
3	61	57	3	0
4	53	41	1	0
5	55	49	1	1
6	53	49	0	0
Infrarenal aortic cross-clamping				
7	58	39	3	0
8	65	54	5	3
9	68	76	0	0
10	56	56	4	1
11	64	56	2	2
12	65	40	2	1

this period. Doing so, we obtained the change in $\bar{S}\bar{V}O_2$ for a twofold increase in $\dot{V}O_2$. These normalized values of $\bar{S}\bar{V}O_2$ changes were calculated separately in the six patients whose preoperatively measured ejection fractions were higher than 50% and in the six patients whose preoperative ejection fractions were lower than 50%. Comparison between these two groups was performed by applying Student's *t*-test.

Results

Pertinent clinical data on the two groups of patients are given in Table 1. The time-course of changes in $\dot{V}O_2$, $\bar{S}\bar{V}O_2$, core temperature, and CO is presented in Figure 1. Before anesthesia, all measured values were similar in both groups of patients. After induction of anesthesia, $\dot{V}O_2$ decreased on average by 28%. Throughout anesthesia, except for the period of aortic cross-clamping, $\dot{V}O_2$ remained fairly stable, as shown by the low value of its variation coefficient (SD/mean) calculated for each patient: $7.1\% \pm 0.4\%$. There was also good stability of hemoglobin concentrations, with individual variation coefficients ranging from 2.2% to 12.9% (mean $9.9\% \pm 1.8\%$). SpO_2 remained above 96%. Core temperature was stable, between 34.4 and 35.3°C. Contrasting with the relative stability of $\dot{V}O_2$, SpO_2 , and hemoglobin, large variations of CO were observed, especially after induction of anesthesia, traction on the mesentery or bowel manip-

ulation (10), and transient episodes of hypovolemia. In patients 2 and 4 high values of CO were observed after the phase of renal artery repair. Figure 2 shows the fitted lines of correlation obtained in each patient during this period between CO and $\bar{S}\bar{V}O_2$. At least 12 simultaneous measurements of both variables were made for each patient. The mean individual correlation coefficient was 0.86 ± 0.03 (range, 0.61–0.94).

During supraceliac aortic cross-clamping (19 ± 3 min), the following significant changes were observed (by comparison with values measured immediately before clamping): a $28\% \pm 3\%$ decrease in CO, a $49\% \pm 6\%$ decrease in $\dot{V}O_2$, and a $11\% \pm 2\%$ increase in $\bar{S}\bar{V}O_2$ (Figure 1). During infrarenal aortic cross-clamping (47 ± 5 min), the only significant change was an $11\% \pm 3\%$ decrease in $\dot{V}O_2$. Declamping led in both groups to an immediate and dramatic decrease in $\bar{S}\bar{V}O_2$, lasting for only 4–6 min. There was also a transient increase in $\dot{V}O_2$ slightly above pre-clamping values, lasting for 2–6 min. Arterial blood lactate increased soon after declamping and remained at a supranormal level up to the end of anesthesia (Table 2).

In the postoperative period, $\dot{V}O_2$ increased gradually, reaching a maximum during the second hour, then returned progressively toward preoperative values (Figure 1). The same pattern of evolution was observed for CO. The maximum individual increase in $\dot{V}O_2$ ranged from 74% to 296% of values measured at the beginning of this period. The largest increases in $\dot{V}O_2$ were observed in the nine patients (four in the infrarenal cross-clamping group and five in the other group) who presented clinical evidence of shivering. There was no significant change in blood lactate concentrations (Table 2). $\bar{S}\bar{V}O_2$ changed in a direction opposite to that of $\dot{V}O_2$ and CO. In each patient, the minimal value of $\bar{S}\bar{V}O_2$ coincided with the peak value of $\dot{V}O_2$.

As shown in Figure 3, $\bar{S}\bar{V}O_2$ changes were more significant in the six patients with preoperatively measured left ventricular ejection fraction less than 50% than in the six patients with ejection fraction greater than 50%. We found no relationship between postoperative $\bar{S}\bar{V}O_2$ changes and the existence of abnormalities on the preoperative thallium scan.

Discussion

The findings of this study show that the factors of variation of $\bar{S}\bar{V}O_2$ are clearly different during the three periods associated with abdominal aortic surgery that were considered.

During the anesthetic period when the aorta was not clamped, changes in $\bar{S}\bar{V}O_2$ were related to changes in CO. These results are consistent with those obtained by Jamieson et al. during cardiac surgery (11),

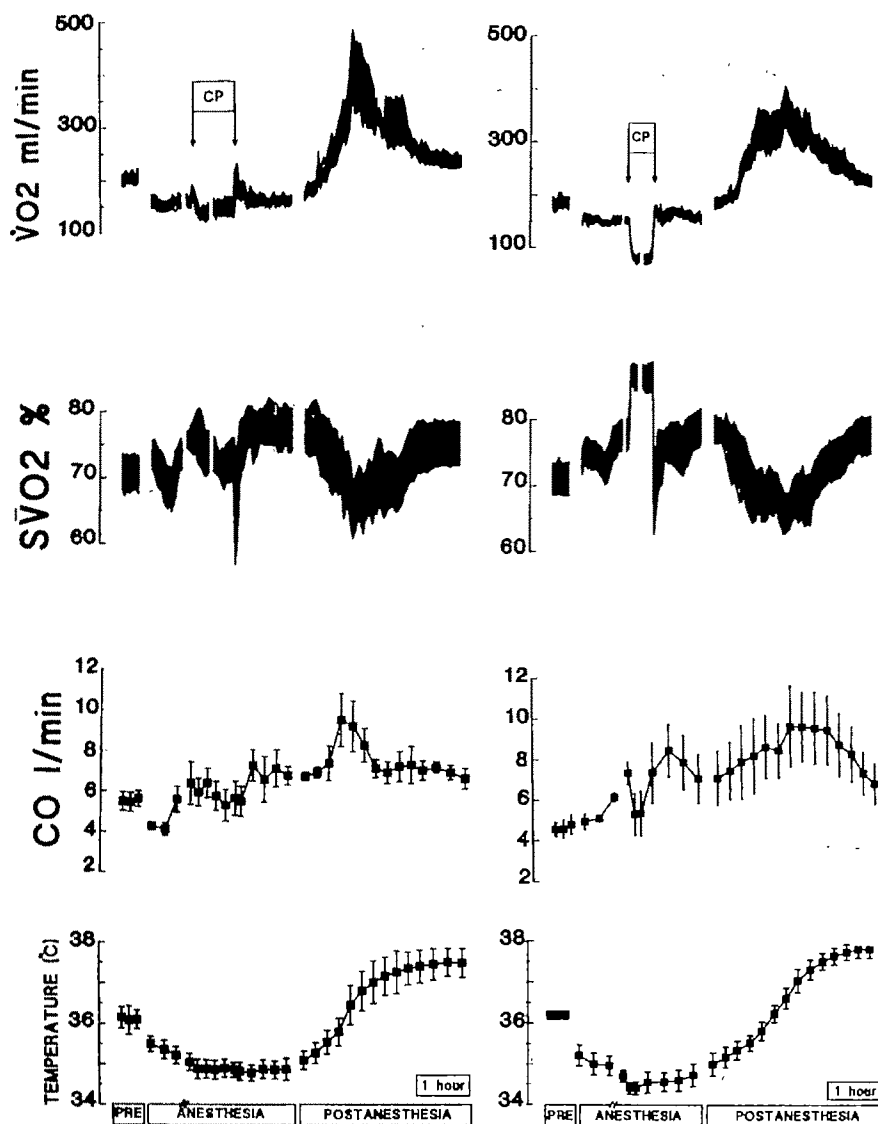


Figure 1. Changes in oxygen uptake ($\dot{V}O_2$), mixed venous oxygen saturation ($\bar{S}vO_2$), core temperature (TEMPERATURE), and cardiac output (CO) before (PRE), during (ANESTHESIA), and after (POSTANESTHESIA) anesthesia for abdominal aortic aneurysm repair. Left panel: six patients having infrarenal aortic cross-clamping (CP); right panel: six patients having supraceliac aortic cross-clamping (CP). As the durations of anesthesia and of aortic cross-clamping were different among patients, some values are not represented in the figure to synchronize individual recordings: from the 75th minute after induction of anesthesia to the 5th minute preceding aortic cross-clamping, during the middle of the aortic cross-clamping period, and from the 75th minute after the release of aortic cross-clamping to the end of anesthesia.

but are in contrast with those of Shenag et al. who did not observe any significant correlation between CO and $\bar{S}vO_2$ during the most critical periods of thoracic aortic surgery (12). An appropriate mathematical model is needed to correlate CO and $\bar{S}vO_2$. In our study, we chose a hyperbolic model. This model takes into account the physiologic relationship between CO and $\bar{S}vO_2$, which can be easily derived by rearranging the Fick equation.

From a practical point of view, the good relationship found between CO and $\bar{S}vO_2$ suggests that monitoring of CO could be achieved by monitoring of $\bar{S}vO_2$. However, some caution should be taken in the interpretation of our results. First, as shown in Figure 2, one absolute value of $\bar{S}vO_2$ found in a given patient does not allow for the deduction of one absolute value of CO. Second, the accuracy of changes in $\bar{S}vO_2$

as an indicator of changes in CO seems to depend on the value of $\bar{S}vO_2$ (Figure 2). Below a value of less than approximately 75%, the accuracy is adequate as small changes in CO are associated with large changes in $\bar{S}vO_2$. Above this value, the accuracy is poor as large changes in CO are required to induce significant changes in $\bar{S}vO_2$.

During infrarenal aortic clamping, decreases in $\dot{V}O_2$ (~11%) and CO (not statistically significant) were modest. Although large differences in oxygen extraction were likely to occur between normally perfused and underperfused tissues, the stable value of $\bar{S}vO_2$ we observed during this period suggests that whole body oxygen extraction was not significantly affected. During supraceliac aortic cross-clamping, decreases in $\dot{V}O_2$ and CO were more marked. The increase in $\bar{S}vO_2$ may be explained by the fact that the reduction

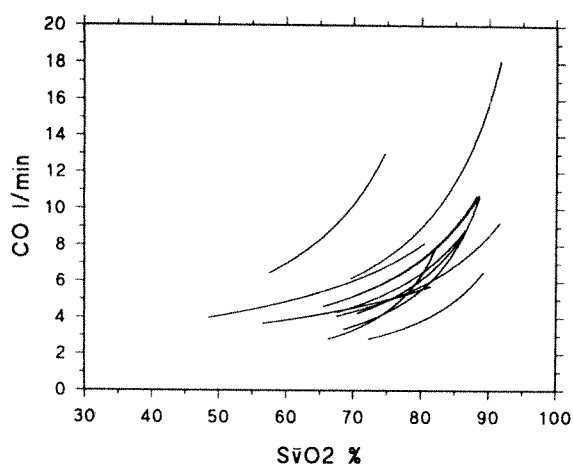


Figure 2. Individual fitted lines of correlation between cardiac output (CO) and mixed venous oxygen saturation (SvO_2) during the period of general anesthesia except for the period of aortic cross-clamping. For clarity, individual data points (12–25 for each patient) are not represented. Measured values of CO ranged from 2.6 to 17.4 L/min. The variation coefficient of CO (sd/mean) during this period ranged among patients from 22.6% to 34.7%.

in $\dot{V}\text{O}_2$ (–49%) exceeded that of CO (–28%), thus decreasing whole body oxygen extraction.

The immediate but short-lasting decrease in SvO_2 after release of aortic clamping is likely to reflect the recirculation of desaturated blood originating from tissues that were underperfused during the period of clamping. After unclamping, the moderate increases in $\dot{V}\text{O}_2$ and blood lactate in the two groups of patients suggest that the oxygen deficit incurred during both levels of cross-clamping was of the same order.

During the postoperative period, as in all previous studies during which changes in CO were associated with changes in $\dot{V}\text{O}_2$ (13–15), we failed to observe any correlation between SvO_2 and CO. In fact, in contrast to that noted during the operative period, SvO_2 actually decreased when CO increased. This pattern was related to the physiologic adaptations to the increased oxygen demand that take place during the immediate postoperative period (16). In healthy subjects (17) and in patients with chronic cardiac failure (18), increases in both CO and oxygen extraction

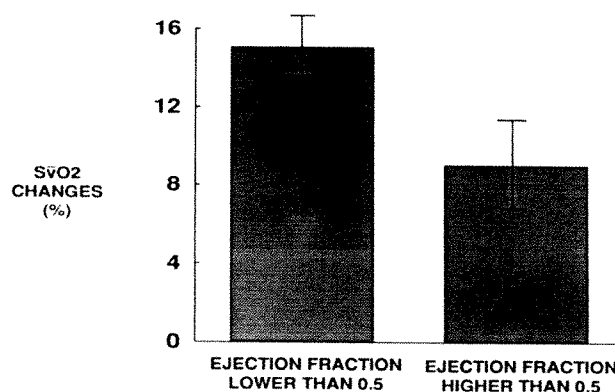


Figure 3. SvO_2 changes during the postoperative period in the six patients whose left ventricular ejection fraction was preoperatively less than 50% and in the six patients whose preoperative ejection fraction was greater than 50%.

occur to meet the increase in oxygen demand associated with muscular exercise. Our data show that both mechanisms are also brought into play during the recovery period from general anesthesia. We hypothesized that increases in CO and oxygen extraction are not involved to the same extent according to the patient's myocardial status. We therefore examined SvO_2 changes, an index of oxygen extraction for a given increase in $\dot{V}\text{O}_2$, in patients classified on the basis of the results of preoperative radionuclear imaging. Abnormalities on dipyridamole-thallium imaging failed to influence the value of this index during the first three postoperative hours. Conversely, differences among patients regarding normalized SvO_2 changes appeared when the value of ventricular ejection fraction was considered. The fact that the postoperative decrease in SvO_2 was more marked in the patients with a low value of ejection fraction suggests that the more severe the myocardial impairment, the more elevated peripheral oxygen extraction was. However, the influence of the level of aortic cross-clamping cannot be excluded, as four of the six patients with depressed left ventricular function had supraceliac clamping, whereas only two patients having infrarenal clamping had depressed left ventricular

Table 2. Serum Lactate Concentration During Anesthesia and the Immediate Postoperative Period

	2 Min before aortic declamping (mM/L)	2 Min after aortic declamping (mM/L)	Skin closure (mM/L)	90 Min after the end of anesthesia (mM/L)	180 Min after the end of anesthesia (mM/L)
Supraceliac aortic cross-clamping (n = 6)	1.5 ± 0.1	4.4 ± 0.8 ^a	2.6 ± 0.3 ^a	3.3 ± 0.4 ^a	2.6 ± 0.4 ^a
Infrarenal aortic cross-clamping (n = 6)	1.3 ± 0.2	4.1 ± 0.5 ^a	2.8 ± 0.6 ^a	2.4 ± 0.7 ^a	2.4 ± 0.6 ^a

Values are mean ± SE.

^aP < 0.05 vs value measured 2 min before aortic declamping.

function. In our patients, the fact that postoperative blood lactate levels remained stable indicates that even in the case of a moderately impaired myocardial function, adequate tissue oxygenation was still ensured.

In conclusion, excluding the period of aortic clamping, general anesthesia with fentanyl, atracurium, nitrous oxide, and isoflurane is associated with moderately stable values of $\dot{V}O_2$, SpO_2 , and hemoglobin. Under these conditions, CO is the main factor of variation of $\bar{S}vO_2$. During supraceliac aortic cross-clamping, the magnitude of the decrease in $\dot{V}O_2$ is more marked than that of CO, which leads to an increase in $\bar{S}vO_2$. No significant change in $\bar{S}vO_2$ is observed during infrarenal aortic cross-clamping. Finally, during the first three postoperative hours, when both CO and peripheral oxygen extraction increase to match the enhanced oxygen demand of the body, $\bar{S}vO_2$ changes are greater in the case of compromised myocardial function.

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Effects of Local Anesthesia on Recovery After Outpatient Arthroscopy

Ian Smith, FFARCS, Jan Van Hemelrijck, MD, Paul F. White, PhD, MD,
and Robert Shively, MD

Departments of Anesthesia and Surgery, Washington University School of Medicine, St. Louis, Missouri

The effects of intraarticular bupivacaine administration on postoperative pain and mobilization were evaluated in 97 healthy outpatients undergoing knee arthroscopy under general anesthesia. After completion of the operation, which was performed using a standardized general anesthetic technique, the patient's knee was injected with 30 mL of either 0.5% bupivacaine or saline solution (control), according to a randomized, double-blind protocol. Although there were no statistically significant differences in the patient's assessment of postoperative pain, patients receiving bupivacaine required significantly less opioid analgesic medication in the postoperative period.

More importantly, ambulation occurred more rapidly in those patients treated with bupivacaine (versus saline solution), permitting them to be discharged earlier than the control patients (145 ± 51 min vs 173 ± 50 min). No adverse effects were noted after the 150-mg intraarticular dose of bupivacaine. On the day after operation, no differences in physical activity or analgesic requirements were detected between the two treatment groups. In conclusion, bupivacaine reduced the opioid requirements and facilitated earlier mobilization after knee arthroscopy without altering the patients' perception of postoperative pain.

(Anesth Analg 1991;73:536-9)

Local anesthetics are popular adjuvants during outpatient anesthesia because they can provide significant intraoperative and postoperative analgesia after a variety of surgical procedures. Although many orthopedic surgeons inject bupivacaine into the intraarticular space after arthroscopic knee surgery, most published studies have failed to demonstrate a significant decrease in postoperative pain (1-3). The lack of an observed analgesic effect may have been the result of using only 0.25% bupivacaine. Higher concentrations of bupivacaine have not been used because of concerns regarding its potential toxicity (i.e., due to rapid uptake through the synovium); however, plasma bupivacaine levels measured after the intraarticular administration of 100 mg of bupivacaine were below toxic levels (2).

We assessed the efficacy of bupivacaine, 150 mg (30 mL of 0.5%), in a double-blind, placebo-controlled study. In addition to assessing postoperative pain relief, we also evaluated the effect of local anesthesia on early mobilization after ambulatory arthroscopy.

Methods

Written informed consent was obtained from 97 healthy outpatients scheduled to undergo arthroscopic knee surgery under general anesthesia. Patients were randomly assigned to one of two treatment groups according to a double-blind protocol, which was approved by the Human Studies Committee of Washington University School of Medicine. Patients with a history of hypersensitivity to local anesthetic agents were excluded from participation in the study. All patients fasted for at least 6 h before the operation and received no preanesthetic medication. Before induction of anesthesia, patients completed baseline 100-mm visual analogue scales (VAS) for pain, sedation, and nausea. These VAS scores ranged from 0 = none to 100 = maximum.

After insertion of an intravenous cannula and placement of routine intraoperative monitoring devices, patients received a standardized general anesthetic consisting of 2.5 mg/kg of intravenous propofol for induction followed by a variable-rate propofol infusion ($75-180 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) and by 67% nitrous oxide in oxygen. At the end of the operation, the patient's knee joint was injected through one of the arthroscopy portals with 30 mL of either saline solution or 0.5% bupivacaine as determined by a computer-

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Address correspondence to Dr. White, Division of Clinical Research, Department of Anesthesiology, Washington University School of Medicine, Box 8054, 660 South Euclid Avenue, St. Louis, MO 63110.

generated random number sequence. The study medications were supplied by the hospital pharmacy in an unmarked syringe; and neither the anesthesiologist, surgeon, nor patient was aware of the treatment administered. On completion of the operation, the infusion of propofol and nitrous oxide were discontinued simultaneously. The times from the end of anesthesia until awakening (defined as spontaneous eye opening), sitting up in a chair, tolerating oral fluids, ambulating, being judged "fit for discharge," and hospital discharge were recorded by a blinded observer. Mobilization was facilitated by the use of crutches (all patients received instruction in their use preoperatively). Patients were encouraged to sit up and to begin the mobilization process whenever they felt able to, without any predefined time constraints. Patients were considered to be fit for discharge when they were oriented to time and place, had stable vital signs on sitting up and mobilizing, could void urine, and were able to ambulate (with the use of crutches).

A standard three-lead electrocardiogram was used to monitor the heart rate and rhythm during the first 60 min in the recovery room. Postoperative pain was treated with intravenous bolus doses of 25 μ g of fentanyl. The patient's postoperative requirements for analgesic and antiemetic medications were recorded. The patient's assessment of postoperative sedation, pain, and nausea was again recorded using the 100-mm VAS at 15-min intervals after operation for the first hour of recovery and at discharge. The patients were contacted the day after operation by a research nurse (also blinded to the technique) who inquired about their use of analgesic medication and physical condition after discharge from the outpatient surgery center.

Data are expressed as mean \pm standard deviation. Continuous variables were analyzed using analysis of variance, whereas descriptive variables were analyzed using the χ^2 -test. A *P* value less than 0.05 was considered to be statistically significant.

Results

A total of 49 patients received intraarticular 0.5% bupivacaine, and 48 received a similar volume of saline solution. There were no significant differences in age, sex distribution, weight, duration of surgery, and total dose of propofol administered (Table 1) between the two treatment groups. Both groups of patients had similar awakening times from anesthesia; however, later recovery events occurred progressively earlier in those patients who received intraarticular bupivacaine (Figure 1). Patients who received bupivacaine were discharged an average of 30 min earlier than those receiving saline solution. Despite the improvement in mobility in the bupivacaine-

Table 1. Demographic Characteristics of the Two Treatment Groups

Variables	Saline solution	0.5% Bupivacaine
Number (n)	48	49
Age (yr)	36 \pm 12	35 \pm 14
Sex (M/F)	34/14	31/18
Weight (kg)	80 \pm 16	78 \pm 14
Duration of operation (min)	56 \pm 16	53 \pm 19
Total propofol (mg)	661 \pm 172	617 \pm 198

Values are mean \pm SD (or numbers).

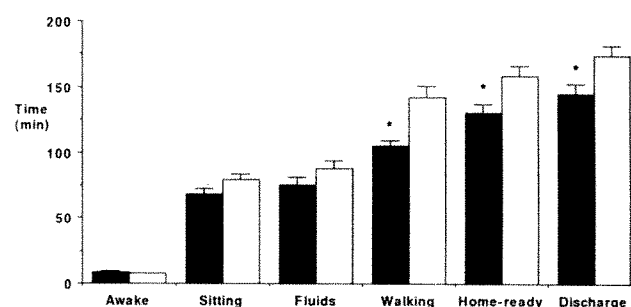


Figure 1. Times from discontinuation of anesthesia until the patients were awake, able to sit up in a chair (sitting), tolerate oral fluids (fluids), ambulate (walking), were judged "fit for discharge" (home-ready), and were discharged. Dark bars represent 0.5% bupivacaine, light bars represent saline (control) group. Values are mean \pm SEM. **P* < 0.05, from control group.

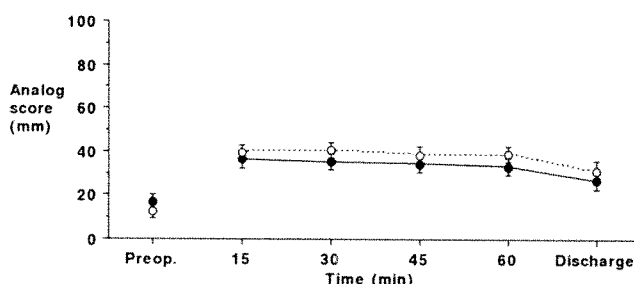


Figure 2. Pain visual analogue scales before (Preop.) and postoperatively at 15, 30, 45, and 60 min after arriving in the recovery room as well as at the time of discharge for the two treatment groups (—●—, 0.5% bupivacaine; - -○-, saline). Values are mean \pm SEM.

treated group, there was no difference in the patients' assessment of their postoperative pain (Figure 2). This observation was unchanged when patients who had received opioid analgesic medication in the recovery room before completion of VAS were excluded from the analysis.

Significantly fewer of the bupivacaine-treated patients required an opioid analgesic medication postoperatively, and the total dose of analgesic medication was also significantly lower (Table 2). When contacted by telephone the following day, almost all patients had some pain and similar numbers in each

Table 2. Postoperative Analgesic Requirements of the Two Treatment Groups

Variables	Saline solution	0.5% Bupivacaine
Required postoperative fentanyl (% , n)	57, 26	37, 18*
PACU fentanyl dose (μ g)	51 \pm 71	27 \pm 39*
First analgesia (min)	26 \pm 16	27 \pm 21
Oral analgesic at home (% , n)	65, 30	61, 30

Values are mean \pm SD or percentage (number of patients).*Significantly different from the saline group, $P < 0.05$.

group required an oral analgesic medication. There was no difference in the patients' perceived level of postoperative sedation or nausea (by VAS) in the two treatment groups. Nausea was not a significant problem after these outpatient arthroscopic procedures, with only four patients in each treatment group requiring postoperative antiemetic medication. There was no correlation between the degree of postoperative nausea and the postoperative dose of opioid analgesic medication. No clinical signs or symptoms of local anesthetic toxicity (e.g., cardiac dysrhythmias) were noted in any patient during the early postoperative period.

Discussion

Previous studies (1-3) have failed to demonstrate a significant decrease in postoperative pain scores when 0.25% bupivacaine was administered intraarticularly after arthroscopic surgery. In one study (4), 0.25% bupivacaine reduced postoperative pain after arthroscopic meniscectomy. However, these authors only compared pain scores in those patients who required postoperative analgesia, which may explain the difference between this and other studies. In keeping with most of the previously published studies, we also failed to demonstrate a significant decrease in postoperative pain scores despite the use of a higher concentration of bupivacaine (0.5%).

In contrast to a previous report in which 0.25% bupivacaine failed to decrease postoperative opioid requirements in an adolescent population (5), patients who received 0.5% bupivacaine were less likely to require postoperative opioid medication and also required a lower average dose of the analgesic medication. The difference in these two observations may result from the higher dose of bupivacaine used in our study. Alternatively, the difference may simply reflect the fact that an insufficient number of patients were enrolled in the previous investigation (5).

More importantly, intraarticular 0.5% bupivacaine resulted in earlier ambulation (105 \pm 29 min vs 142 \pm

51 min) and earlier discharge (145 \pm 51 min vs 173 \pm 50 min) from our outpatient facility. The only previous study addressing the issue of postoperative mobilization failed to detect any benefit from 0.25% bupivacaine (3). As a patient's pain presumably would have been enhanced by mobilization, differences in the pain scores may have been obscured because patients who received bupivacaine were able to mobilize earlier. However, this would not explain the lack of a difference in pain scores before mobilization. Although it is possible that the peak effect of bupivacaine was delayed such that ambulation was improved without affecting earlier pain scores, this is not consistent with the onset time of intraarticular bupivacaine when it is used to provide analgesia during arthroscopies performed under local anesthesia (6). The patient's VAS pain scores may have reflected other causes of postoperative pain (e.g., hip and back pain from positioning in the operating room and pain from manipulating the leg), which were unaffected by the intraarticular bupivacaine. Unfortunately, our study design did not address the specific site of the patient's pain. Consistent with its known duration of action, the effects of bupivacaine were not apparent the following day. Almost all patients experienced some degree of pain the day after surgery, for which a little over half of the patients in each group required oral analgesic medication.

In the control group of patients, the larger requirement for postoperative opioid analgesia might have been expected to result in a higher incidence of postoperative nausea in this outpatient population. However, the incidence of nausea (as assessed by VAS) and the requirement for antiemetic drugs were very low in both treatment groups. This finding might be a result of the anesthetic technique used in our study (i.e., propofol-nitrous oxide) as a 25% incidence of postoperative nausea was reported in an arthroscopic surgery study that used general anesthesia with volatile anesthetics (7). Propofol has previously been reported to have antiemetic effects (8).

In summary, although intraarticular 0.5% bupivacaine did not significantly decrease the patient's perception of pain, the local anesthetic facilitated early mobilization after outpatient knee arthroscopy.

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Efficacy of Esmolol Versus Alfentanil as a Supplement to Propofol-Nitrous Oxide Anesthesia

Ian Smith, BSc, MBBS, FFARCS, Jan Van Hemelrijck, MD, and Paul F. White, PhD, MD

Department of Anesthesiology, Washington University School of Medicine, St. Louis, Missouri

In 97 outpatients undergoing ambulatory arthroscopic procedures, we compared esmolol with alfentanil when used to supplement propofol-N₂O-atracurium anesthesia according to a randomized, double-blind protocol. After an initial intravenous dose of 16 µg/kg alfentanil, or 2 mg/kg of esmolol, a variable-rate infusion of alfentanil or esmolol was administered to maintain a stable heart rate. After induction of anesthesia with 2.5 mg/kg of propofol, mean arterial pressure decreased to a larger extent in the alfentanil-treated patients. Although heart rate and mean arterial pressure increased in both groups after tracheal intubation, alfentanil more effectively blunted the hemodynamic response to this stimulus. Maintenance of anesthesia was adequate in both treatment groups. After discontinuation of anesthesia, patients in the esmolol group opened their eyes earlier (7.2 ± 2.4 min vs 9.8 ± 4.6 min) than those in the alfentanil group. Esmolol-treated patients also

reported less sedation in the first 15 min of recovery than those receiving alfentanil. However, there were no differences in times to ambulation and discharge between the groups. Esmolol-treated patients reported more postoperative pain for the first 15 min of recovery and more esmolol-treated patients required postoperative opioid analgesia than those treated with alfentanil. There were no significant differences in the incidences of nausea and vomiting between the two groups. The authors conclude that esmolol may be used in place of alfentanil to supplement propofol-N₂O-atracurium anesthesia in outpatients undergoing arthroscopic procedures. However, hemodynamic responses to tracheal intubation were larger with esmolol, and avoidance of alfentanil did not decrease the incidence of postoperative nausea and vomiting in this outpatient population.

(Anesth Analg 1991;73:540-6)

Acute hemodynamic responses to tracheal intubation and surgical stimulation are generally considered to be undesirable. Opioid analgesics are commonly used as adjuvants during general anesthesia to minimize acute increases in arterial blood pressure and in heart rate (HR) during anesthetic induction and maintenance periods. However, opioids can delay awakening from anesthesia, impair psychomotor performance, and increase the incidence of postoperative nausea and vomiting. These factors can contribute to a delayed discharge after ambulatory surgery.

Esmolol, a β -adrenoceptor antagonist, is capable of attenuating the tachycardia and hypertension associated with tracheal intubation (1). This raises the

possibility of using a β -blocker as an alternative to an opioid analgesic to maintain hemodynamic stability, and thereby to avoid opioid-related side effects. We designed this randomized, double-blind study to compare the effects of esmolol (a rapid and short-acting β -blocker) and alfentanil (a rapid and short-acting opioid analgesic) on intraoperative hemodynamic stability and recovery variables when used to supplement propofol-N₂O anesthesia.

Methods

After obtaining written, informed consent, 97 healthy (ASA physical status I and II) outpatients undergoing elective arthroscopic surgical procedures were randomly assigned to one of two anesthetic treatment groups according to a double-blind protocol approved by the Human Studies Committee at Washington University School of Medicine. Patients with a history of asthma (or reactive airway diseases) or hypersensitivity reactions to opiates were excluded. All outpatients fasted for at least 6 h and were not premedicated on arrival in the operating room.

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Address correspondence to Dr. White, Division of Clinical Research, Department of Anesthesiology, Washington University School of Medicine, Box 8054, 660 South Euclid Avenue, St. Louis, MO 63110.

After placement of an intravenous catheter, routine monitoring devices were applied (including a blood pressure cuff, electrocardiogram, precordial stethoscope, and pulse oximeter). Mean arterial blood pressure (MAP) and HR were recorded using an automated device (Dinamap, Critikon, Tampa, Fla.) before administration of any drug (baseline) at 1-min intervals from induction until skin incision and subsequently at 5-min intervals for the remainder of the procedure. Before intravenous induction of anesthesia, 2–3 mg of *d*-tubocurarine, 50 mg of lidocaine, and 0.3 mg/kg of propofol were administered to all patients. After breathing 100% oxygen, a 0.2-mL/kg bolus of either esmolol (2 mg/kg) or alfentanil (16 μ g/kg) was infused at a rate of 3 mL/min according to the randomization sequence. The study drugs were supplied by the hospital pharmacy in unmarked 60-mL syringes containing either 80 μ g/mL of alfentanil or 10 mg/mL of esmolol and were administered using a syringe-type infusion pump (Bard InfusOR, C.R. Bard Inc., North Reading, Mass.). Both the patient and anesthesiologist were blinded to the study medication. The dose of each of the two study medications was chosen based on studies in the published anesthesia literature, and the concentration was adjusted such that an approximately "equipotent" solution (with respect to hemodynamic effects) would be administered to allow proper blinding of the study.

Two minutes after the start of the study drug administration, anesthesia was induced with a bolus of 2.5 mg/kg of propofol using a second Bard InfusOR syringe pump. After loss of the eyelash reflex, 1.5 mg/kg of succinylcholine was intravenously administered to facilitate tracheal intubation. Anesthesia was maintained with propofol and 67% nitrous oxide (N₂O) in oxygen at an initial infusion rate of 0.16 mg·kg⁻¹·min⁻¹ and was subsequently titrated to maintain an adequate "depth of anesthesia" as judged by blood pressure responses to surgical stimuli. Purposeful movements by the patient were treated with small bolus doses of 0.3 mg/kg of propofol administered intravenously in addition to increasing the propofol infusion rate in increments of 50%–100%. The study drug infusion rate was initially maintained at 0.01 mL·kg⁻¹·min⁻¹ (i.e., 100 μ g·kg⁻¹·min⁻¹ of esmolol or 0.80 μ g·kg⁻¹·min⁻¹ of alfentanil). This was decreased to 0.0025 mL·kg⁻¹·min⁻¹ after intubation and was subsequently adjusted to maintain HR within 15% of the preoperative baseline values.

Ventilation was controlled at a minute volume sufficient to maintain PACO₂ values in the range of 34–38 mm Hg. Neuromuscular blockade was provided with small bolus doses of 10–20 mg of atracurium, administered intravenously as needed. The

atracurium dose provided sufficient muscular relaxation to facilitate operation, while not preventing purposeful movements in response to surgical stimuli in the presence of inadequate anesthesia.

After completion of the operation, residual neuromuscular block was antagonized with 0.05 mg/kg of neostigmine and 0.01 mg/kg of glycopyrrolate, as necessary. The study drug and propofol infusions were terminated when the N₂O was discontinued on completion of the arthroscopy. The total doses of propofol and study drug were recorded, as were the number of supplemental bolus doses of propofol. After discontinuation of anesthesia, the times of spontaneous eye opening and of arrival in the postanesthesia care unit (PACU) were recorded. Recovery was further evaluated by recording the times at which patients were first able to sit up in a chair, tolerate oral fluids, and walk to the bathroom and the time at which they were judged to be fit for discharge (i.e., "home ready").

The incidence of nausea and vomiting and the requirement for antiemetic medication were also recorded. Postoperative analgesic requirements were noted; pain, nausea, and sedation were further evaluated using 100-mm visual analogue scales (VAS) at 15, 30, 45, and 60 min after arriving in the recovery room, with values compared with preanesthesia (baseline) values. Visual analogue scale scores ranged from 0 = none to 100 = maximal/most severe. All assessments in the PACU were made by a trained nurse observer who was blinded to the study medication used.

Continuous variables were analyzed using analysis of variance (ANOVA), with repeated measures used to assess changes over time. Positive findings with ANOVA were confirmed by using Student's two-sided, unpaired *t*-tests for comparisons between groups and paired *t*-tests for comparisons over time within groups. In all cases, Bonferroni's correction for multiple comparisons was applied. To evaluate the descriptive variables, χ^2 -tests were used, with *P* values less than 0.05 considered to be statistically significant.

Results

There were no significant differences between the two groups of outpatients in age, weight, sex, type of procedure, duration of operation, and dosage of anesthetic and muscle relaxant drugs (Table 1). In addition, similar volumes of study drugs were infused during the operation in both groups.

The intraoperative hemodynamic changes are summarized in Figure 1. After induction of anesthesia, there was a decrease in both HR and MAP. Heart rate decreased more rapidly in the esmolol group,

Table 1. Demographic Characteristics of the Two Treatment Groups

Variables	Alfentanil	Esmolol
Total number (n)	50	47
Age (yr)	36 ± 13	37 ± 14
Sex (M/F)	34/16	31/16
Weight (kg)	80 ± 14	79 ± 14
Arthroscopic site		
One knee	48	44
Both knees	1	1
Shoulder	1	2
Duration of operation (min)	60 ± 19	57 ± 20
Study drug volume used (mL)	34 ± 8	36 ± 10
Total alfentanil or esmolol (mg)	2.72 ± 0.64	360 ± 100
Required propofol bolus (n)	19	41 ^a
Number of boluses administered	1.7 ± 1.5	2.5 ± 1.2 ^a
Total propofol dose (mg)	622 ± 172	693 ± 200
Total atracurium dose (mg)	17.6 ± 10.2	20.7 ± 10.7

Values are mean ± sd (or numbers).

^aSignificantly different from the alfentanil group, $P < 0.05$.

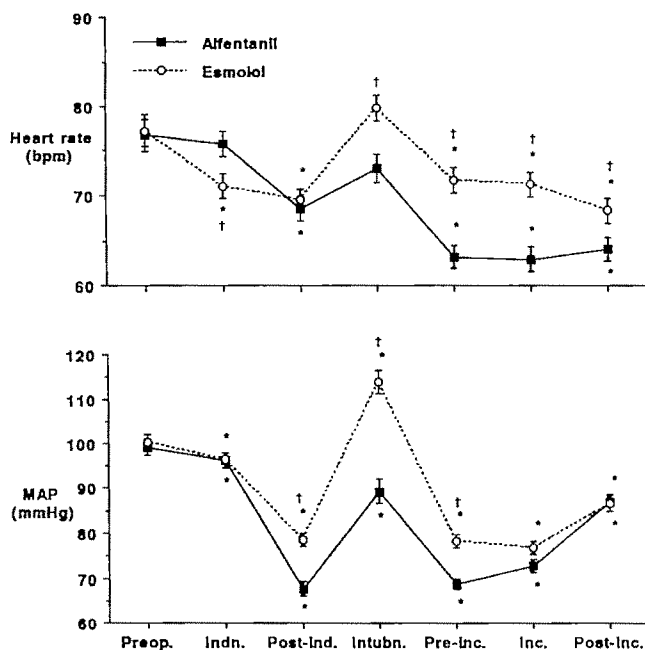


Figure 1. Heart rate (above) and mean arterial blood pressure (below) values from before induction of anesthesia (Preop.), at induction of anesthesia (Indn.), immediately before intubation (Post-ind.), at the peak after intubation (Intubn.), at the lowest point before incision (Pre-inc.), at skin incision (Inc.) and at the postincision peak (Post-inc.). Values are mean ± SEM. * $P < 0.05$, from baseline. † $P < 0.05$, from alfentanil.

being significantly lower than both the baseline (awake) value and the value at the start of induction of anesthesia in the alfentanil group. After anesthetic induction, HR was similar in both groups and significantly lower than baseline values. Mean arterial blood pressure decreased to significantly below baseline values in both groups after induction of anesthe-

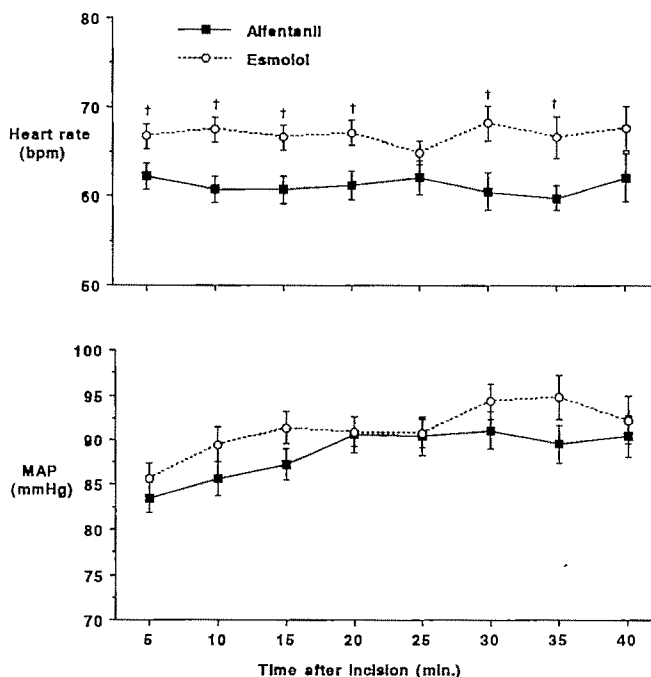


Figure 2. Heart rate (above) and mean arterial blood pressure (below) at 5-min intervals after skin incision (time 0). Values are mean ± SEM. † $P < 0.05$, from alfentanil.

sia; this change was greater in the alfentanil-treated patients. With laryngoscopy and tracheal intubation, HR increased in both groups. Although HR was significantly higher in the esmolol group, it did not differ significantly from awake levels in either group. Mean arterial blood pressure increased significantly from the postinduction value after intubation in both groups. Although MAP exceeded baseline values in the esmolol group, it remained below baseline in the alfentanil group. The difference between the two groups was also statistically significant. Mean arterial pressure returned to preintubation values before skin incision. Heart rate also returned to preintubation levels in the esmolol-treated patients but decreased to below this value in the alfentanil group. Skin incision was associated with a significant increase in MAP (from preincision values) in both groups but remained below baseline values. Heart rate decreased after skin incision in the esmolol group but showed no change in the alfentanil group. Heart rate remained significantly higher in the esmolol group compared with that in the alfentanil-treated patients but was below baseline values in both groups.

After skin incision, HR and MAP both remained stable within 10% of the postsurgical incision levels (Figure 2). There were no statistically significant differences between the two treatment groups in the MAP value. Heart rate values were significantly higher in the esmolol-treated patients at most time points compared with that in the alfentanil-treated patients. However, the HRs in both groups of pa-

Table 2. Heart Rate and Mean Arterial Blood Pressure in the Recovery Room in the Two Treatment Groups

Time	Heart rate (beats/min)		Mean arterial pressure (mm Hg)	
	Alfentanil	Esmolol	Alfentanil	Esmolol
Enter recovery room	73 ± 12	70 ± 11	94 ± 13	88 ± 15*
15 min	65 ± 12	66 ± 11	93 ± 15	93 ± 14
30 min	64 ± 11	63 ± 12	96 ± 15	93 ± 13
60 min	65 ± 13	61 ± 12	95 ± 15	92 ± 12

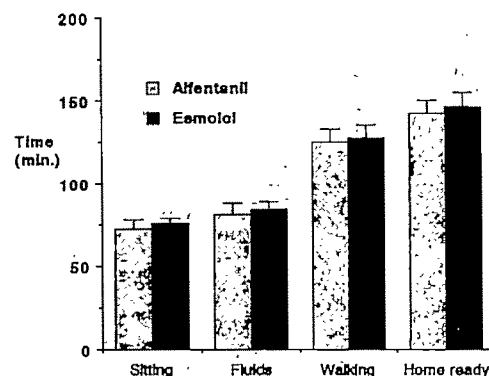
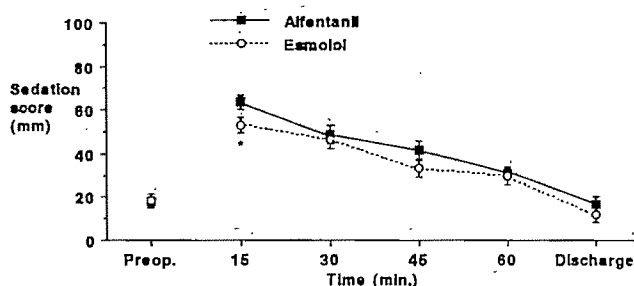
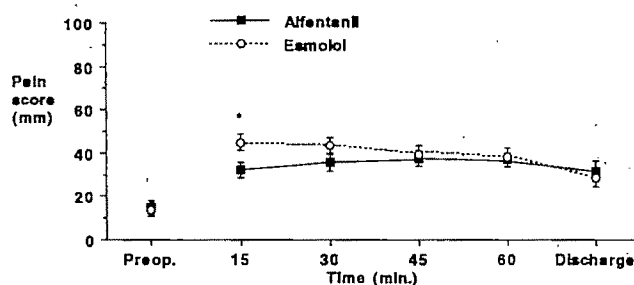
Values are mean ± SD.

*Significantly different from the alfentanil group, $P < 0.05$.

tients were significantly lower than baseline values. Overall, surgical and anesthetic conditions were satisfactory in both treatment groups. However, patients in the esmolol group were more likely to demonstrate clinical signs of "light anesthesia" than those in the alfentanil group as indicated by a larger number of patients who required supplemental bolus doses of 0.3 mg/kg of propofol (41 vs 19, $P < 0.01$) and a higher mean number of bolus doses in those requiring propofol supplementation (2.5 ± 1.2 vs 1.7 ± 1.5 , $P < 0.05$) (Table 1).

Emergence from anesthesia, as measured by the time to spontaneous eye opening, was significantly slower in the patients receiving alfentanil (9.8 ± 4.6 min vs 7.2 ± 2.4 min, $P < 0.01$). Because of this delay in awakening, alfentanil-treated patients also required a longer period of time to reach the recovery room after termination of anesthesia (15 ± 5 min vs 12 ± 3 min, $P < 0.01$). On arrival in the recovery room, patients treated with esmolol had significantly lower MAPs than those treated with alfentanil (Table 2). However, MAP values were similar during the remainder of their PACU stay. There were no significant differences between the two groups in HR at any time in the recovery room (Table 2).

In contrast to the difference in the times to eye opening, intermediate and late recovery variables (measured as the time intervals required for the patients to be able to sit up in a chair, tolerate oral fluids, walk to the bathroom, and to be judged "home ready") did not differ between the two groups (Figure 3). Patients receiving esmolol rated their level of sedation as less than those receiving alfentanil at the 15-min assessment point but not at subsequent evaluation intervals (Figure 4). Patients receiving esmolol also rated their postoperative pain as significantly more severe during the first 15 min in the PACU than those receiving alfentanil (Figure 5). Postoperative opioid analgesic medication was required by 57% of those receiving esmolol compared with 34% of the alfentanil-treated patients ($P < 0.05$). Patients in both groups who required postoperative

**Figure 3.** Times from discontinuation of anesthesia until the patients were able to sit up (Sitting), tolerate oral fluids (Fluids), ambulate (Walking), and were judged to be fit for discharge (Home ready). Values are mean ± SEM.**Figure 4.** Change in visual analogue scores for sedation compared with preoperative (Preop.) values after 15, 30, 45, and 60 min of recovery and at discharge. Values are mean ± SEM. * $P < 0.05$, from alfentanil.**Figure 5.** Change in visual analogue scores for pain compared with preoperative (Preop.) values after 15, 30, 45, and 60 min of recovery and at discharge. Values are mean ± SEM. * $P < 0.05$, from alfentanil.

analgesics rated their pain during the first 45 min of evaluation as significantly more severe than those who did not require analgesic medication. Excluding those patients who had received analgesic medication before completing the pain VAS did not alter the differences between the alfentanil and esmolol groups. However, there were significant differences between the groups if analgesic medication had already been administered before completing the VAS. Local anesthetic was instilled into the knees of 24

Table 3. Nausea Visual Analogue Scores and Percentage of Patients Requiring Antiemetic Medication in the Two Treatment Groups

Time	Alfentanil	Esmolol
Preoperative (baseline)	1 ± 3	2 ± 5
Postoperative		
15 min	8 ± 19	11 ± 17
30 min	9 ± 20	9 ± 15
45 min	9 ± 21	9 ± 16
60 min	8 ± 20	9 ± 17
Discharge	10 ± 24	5 ± 17
Antiemetic requirement (%)	12	6

Values are mean ± SD.

patients (49%) in the alfentanil group and of 22 patients (50%) in the esmolol group. The use of local anesthesia had no significant effect on the postoperative pain scores.

There were no significant differences between the two groups in the degree of nausea as assessed by the patients or in terms of PACU requirements for antiemetic medication (Table 3). Overall, patients were highly satisfied with both anesthetic techniques. When questioned 24 h after discharge, 95% of the esmolol-treated patients and 94% of the alfentanil-treated patients stated that they would be pleased to receive the same anesthetic for a future operation. There were no instances of recall of intraoperative events in either treatment group.

Discussion

Several investigators have demonstrated that esmolol, when compared with placebo, can effectively attenuate the tachycardia and, to a lesser extent, the hypertension associated with tracheal intubation (1-8) and other intraoperative stresses (9). In clinical practice, potent opioid analgesics (e.g., fentanyl and its newer analogues) are often administered to maintain hemodynamic stability during laryngoscopy and tracheal intubation. Unfortunately, the tendency of opioid analgesics to delay recovery, particularly of higher cognitive function (10), as well as to increase the incidence of postoperative nausea and vomiting (11) in outpatients undergoing ambulatory surgical procedures, can significantly delay discharge. A drug capable of rapidly controlling tachycardia and hypertension without prolonged negative inotropic effects would be beneficial for perioperative control of transient hemodynamic responses to surgical stimuli (12). Esmolol compares favorably with fentanyl in its ability to obtund unwanted cardiovascular response to laryngoscopy and tracheal intubation in patients with cardiovascular disease (13,14).

Consistent with previous findings, we found es-

molol to be more effective in preventing the HR from exceeding baseline values after tracheal intubation than in controlling the acute hypertensive response. Both HR and MAP were significantly higher after tracheal intubation in the esmolol group than in the alfentanil-treated patients. However, this greater hemodynamic responsiveness in the esmolol group should probably be balanced against the transient period of hypotension observed after induction of anesthesia in the alfentanil-treated patients.

Because tachycardia-induced myocardial ischemia can occur in patients with coronary artery disease (15), it has been suggested that a rapid and short-acting β -blocking drug, which reduces tachycardia while maintaining coronary perfusion pressure, may be especially beneficial in high-risk patient populations (16). In our healthy outpatients, no evidence of myocardial ischemia was observed in either group during this study. The transient hypotension recorded immediately after induction of anesthesia in the alfentanil group could have been decreased by using a lower dose of either propofol or alfentanil.

Although both study drugs were adequate adjuvants during induction and maintenance of propofol-N₂O anesthesia for outpatient arthroscopic procedures, more patients in the esmolol group needed supplemental bolus doses of propofol. Hemodynamic stability after skin incision was similar in both groups, although esmolol-treated patients had higher mean HR values than those treated with alfentanil. Importantly, the values of hemodynamic variables after skin incision remained significantly less than preoperative baseline values in both treatment groups. The lower MAP values on entering the recovery room in the esmolol group are difficult to explain. However, esmolol has been previously shown to be more effective than alfentanil in preventing hypertensive responses to extubation (17).

In comparing esmolol with a rapid and short-acting opioid analgesic, we were able to demonstrate a significantly shorter time to eye opening with esmolol (vs alfentanil). However, provided that outpatients are adequately observed during the early recovery phase, this difference is probably of limited clinical significance. Nevertheless, the earlier time of transfer to the PACU would facilitate room turnover in a busy ambulatory facility. Although there was a significant difference in the times to eye opening and in the patients' initial evaluation of their degree of postoperative sedation, there were no significant differences between the groups in the later recovery phase or in the time of discharge.

As might have been expected, the analgesic properties of alfentanil persisted into the early postoperative period as evidenced by the lower pain scores recorded by the alfentanil-treated patients during the

first 15 min in the PACU. This was also reflected in the increased requirement for postoperative opiate analgesics in the esmolol group. The lack of a significant difference in pain VAS scores after 15 min is a reflection of the natural time-course of the postoperative pain rather than a modifying effect of the intraoperative analgesic medication. Not surprisingly, postoperative pain was rated higher by patients in both treatment groups who required analgesic medication than by those who did not, and this difference persisted for 45 min. The use of intraarticular local anesthetics had no demonstrable effect on postoperative pain scores, consistent with the findings of other investigators (18-20). Overall, the postoperative requirements for analgesic medication in this outpatient surgical population were minimal, and both groups of outpatients were equally satisfied with their anesthetic technique.

Our failure to demonstrate any significant reduction of postoperative nausea and vomiting after the use of esmolol as an alternative to an opioid analgesic may be due to the intrinsically low incidence of nausea in outpatients undergoing arthroscopic surgery. To detect a statistically significant difference would have required a sample size at least four times larger than our study population. Further studies involving outpatients more susceptible to postoperative nausea and vomiting (e.g., patients undergoing laparoscopic procedures) may show a clinically significant difference between these two drug treatment groups. As propofol may possess antiemetic properties (21), the use of this hypnotic agent could also have masked any differences in emetic sequelae between the two groups. The incidence of postoperative nausea in our study using a propofol-based anesthetic technique was considerably lower than the 25%-45% incidence reported after general anesthesia (using volatile anesthetic-N₂O or opioid analgesic-N₂O-relaxant techniques) for outpatient knee arthroscopy (22-24).

This study could be criticized in that two different infusions had to be titrated simultaneously using clinical end points. Propofol was titrated to minimize signs of inadequate anesthesia (e.g., movement, tearing, swallowing, and acute changes in arterial blood pressure), whereas the study medication was titrated to maintain a stable heart rate. A patient population undergoing an operation associated with minimal perioperative pain was chosen because only half of the patients were to receive intraoperative opioid analgesics. Although a difference in pain scores was reported during the early postoperative period in the two treatment groups, this finding was of little (if any) clinical significance in this surgical population. However, larger differences would be expected after

surgical procedures associated with a greater degree of postoperative pain.

In summary, we have shown that esmolol can be used as an alternative to alfentanil during propofol-N₂O-atracurium anesthesia for ambulatory surgery. However, control of the hemodynamic responses to tracheal intubation was more effectively accomplished with alfentanil. This improved hemodynamic stability during tracheal intubation in the alfentanil group was achieved at the expense of a greater degree of hypotension in the immediate preintubation period. Although alfentanil delayed initial awakening, this study did not demonstrate any adverse effects on later recovery events or discharge times. The use of a potent, rapid-acting opioid analgesic is recommended in situations in which avoidance of a hypertensive response to laryngoscopy and tracheal intubation is of particular importance or when significant postoperative pain is anticipated after ambulatory surgery. On the other hand, esmolol may have advantages when rapid awakening is particularly advantageous (e.g., diagnostic or therapeutic procedures associated with minimal postoperative pain) and when used in outpatients who are sensitive to opioid-related postoperative side effects.

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Patient-Controlled Epidural Analgesia: Demand Dosing

F. Michael Ferrante, MD, Louise Lu, MD, Stephen B. Jamison, MD, and Sanjay Datta, MD

The Pain Treatment Service and the Division of Obstetric Anesthesia, Department of Anesthesia, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

A double-blind, placebo-controlled study was designed to compare the efficacy of demand-dose patient-controlled epidural analgesia (PCEA) with continuous epidural infusion (CEI) for treatment of pain during labor and delivery. Forty patients were randomized to receive 0.125% bupivacaine with fentanyl (2 μ g/mL) through CEI at 12 mL/h or through demand-dose PCEA. Patients using PCEA could demand 3 mL every 10 min without restriction. Analgesia in both groups was comparable. However, there was a significant reduction in total bupivacaine consumption (in milligrams) associated with the use of PCEA (mean \pm SEM: CEI = 76.1 \pm 8.5 mg; PCEA = 42.2 \pm 5.9 mg; 45% reduction). The hourly bupiv-

acaine consumption during the first (CEI = 15.8 \pm 0.6 mg/h; PCEA = 8.8 \pm 1.1 mg/h) and second (CEI = 17.2 \pm 1.2 mg/h; PCEA = 6.8 \pm 1.2 mg/h) stages of labor was also reduced. Overall, this represented a 47% "sparing" of bupivacaine use per hour with PCEA. Similar reductions occurred in the use of fentanyl. The reductions in analgesic requirement, however, were not associated with a reduction in the degree of motor blockade or in the cephalad extent of sensory blockade. A significant dose-sparing effect was associated with the use of demand-dose PCEA as compared with standard CEI for analgesia during labor and delivery.

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The administration of analgesics under patient control has several modes of delivery. The most commonly used mode for administration of intravenous opioids is *demand dosing* wherein a fixed-size dose is self-administered (1). A hybrid of physician-controlled and patient-controlled analgesia is *continuous infusion plus demand dosing*. In this mode, a basal background infusion rate is determined by a physician and can be supplemented by patient demand. Other variants such as infusion-based systems (2) (*infusion demand* and *variable-rate infusion plus demand dosing*) are yet to be studied in detail.

Until now, studies of patient-controlled epidural analgesia (PCEA) for labor and delivery have compared traditional continuous epidural infusions (CEI) with the continuous infusion plus demand-dose mode of PCEA (3,4). Although both authors reported analgesia to be comparable to CEI, Gambling et al. (3) found a modest dose-sparing effect to be associated with continuous infusion plus demand-dose PCEA, whereas Lysak et al. (4) found the dose-sparing effect to be minimal. The choice of mode for PCEA, however, may have significant influence on resultant analgesia and drug usage. The present study reports

the use of pure demand-dose PCEA for pain relief during labor and delivery.

Methods

The study was approved by the institution's Committee for the Protection of Human Subjects from Research Risks. Forty ASA physical status I or II primiparous or multiparous patients in an established labor pattern at term were randomly selected. All patients had requested epidural analgesia for labor and delivery. The criteria for inclusion were a singleton fetus with vertex presentation at term, a pregnancy without complication, no prior history of cesarean delivery, and a conversational fluency in English. Informed consent was obtained from each parturient in the early stage of labor. Patients were then randomized to receive either CEI or PCEA in a double-blind fashion.

Epidural catheterization was performed in the lateral decubitus position after intravenous infusion of at least 1 L of lactated Ringer's solution and pretreatment with 30 mL of oral Bicitra. Using standard techniques, a 20-gauge epidural catheter was placed through a 17-gauge Weiss needle at the L3-4 or L2-3 interspace, threaded 2-3 cm, and taped securely. All patients received an initial dose of 8-13 mL of 0.5% bupivacaine to achieve a level of anesthesia (pin prick) from S-5 to at least T-10.

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Address correspondence to Dr. Ferrante, Pain Treatment Service, Department of Anesthesia, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

Immediately after anesthesia was established, the epidural catheter was connected to an Abbott Life-Care PCA Plus 4100 infuser. All patients received 0.125% bupivacaine and 2 μ g/mL of fentanyl. This combination of analgesics was chosen because it had been shown to minimize local anesthetic usage and motor block (5). Those allocated to the CEI regimen received 12 mL/h (standard infusion rate at our institution), whereas those allocated to receive PCEA were able to self-administer a demand dose of 3 mL every 10 min as needed. No 1- or 4-h dose restrictions were set. Each patient was given a demand button and was instructed to depress the button whenever she began to feel any discomfort. For patients in the CEI group, the button was deactivated (placebo). For patients in the PCEA group, depression of the button delivered demand doses as indicated.

Maternal arterial blood pressure was measured every 5 min for 20 min after epidural insertion and every 30 min after that. Fetal heart rate was continuously monitored throughout labor.

Patients were interviewed every 30 min by an anesthesiologist blinded to the patient's randomization. The adequacy of analgesia was quantitated by means of a 10-cm visual analogue scale. Motor strength (graded according to the Bromage scale [6]) and bilateral sensory anesthesia to pin prick in the midaxillary line were also noted at 30-min intervals. No patient delivered in less than 2 h after beginning to use their individual analgesic modality.

If analgesia was deemed inadequate by the patient at any time, she could receive epidural bolus injections of 0.25% bupivacaine in 3-mL doses every 5 min to a total of 9 mL or until comfortable. Patients were then continued on their original epidural regimen without interruption, until vaginal delivery was accomplished or the patient was taken for cesarean delivery. Any episodes of transient hypotension were treated with intravenously administered fluids and with 5-10-mg intravenous boluses of ephedrine as necessary.

Demographic data and labor characteristics were analyzed using the two-tailed *t* test for unpaired data in the presence of interval data and Fisher's exact test for mode of delivery (nominal) data. Apgar scores were analyzed using the Mann-Whitney U-test. The Friedman χ^2 -test was used to analyze differences in pain scores, degree of motor blockade, and cephalad extent of sensory level.

All volume measures of bupivacaine were converted into milligrams for the purpose of computation. Analgesic consumption was calculated for both the first and second stages of labor. The dose of bupivacaine administered immediately after catheter placement for the initial production of anesthesia was not included in the analyses of first-stage analgesic

usage. This was done to minimize spurious inflation of dosage requirements for shorter courses of labor. All subsequent physician-administered boluses were included in the cumulative totals for the first and second stages. Student's two-tailed *t*-test for unpaired data was used for all statistical analyses of analgesic consumption.

For all statistical analyses, *P* < 0.05 was considered significant.

Results

A tabular display of demographic data and labor characteristics for both study groups is presented in Table 1.

The duration of the first stage of labor (defined as the time between epidural blockade and full cervical dilation) was comparable for the two study groups. Similarly, the duration of the second stage (defined as the time between full cervical dilation and the completion of vaginal delivery or the decision to proceed to cesarean delivery) was also comparable. There was no difference between the study groups with respect to mode of delivery (Table 1). Cervical dilation at placement of the epidural catheter and newborn Apgar scores at 1 and 5 min of life were comparable. Only one newborn (CEI group) had a 1-min Apgar score less than 7 (in actuality, 1-min Apgar = 5). Only one newborn (CEI group) had a 5-min Apgar score less than 9 (in actuality, 5-min Apgar = 8).

Friedman's χ^2 -test demonstrated no difference between groups in pain scores (Figure 1), degree of motor blockade (Figure 2), or cephalad extent of sensory blockade (Figure 3) during the first and second stages of labor. Similarly, repeat analyses with truncation of the first 90 min of data (to correct for the residual effects of the initial bolus of 0.5% bupivacaine) showed no difference between study groups.

Analgesic requirements were markedly reduced by the use of PCEA (Table 2), with similar numbers of patients in both study groups requiring supplemental injections of 0.25% bupivacaine. Despite the similarity in the need for supplemental injections, the total amount of bupivacaine used by the two groups during the study was markedly different (CEI = 76.1 \pm 8.5 mg; PCEA = 42.2 \pm 5.9 mg). This represented a dosage reduction effect of 45% in the PCEA group. When corrected for hourly consumption, the average hourly bupivacaine requirements for the PCEA group in the first and second stages were, respectively, 8.8 \pm 1.1 and 6.8 \pm 1.2 mg/h, as compared with 15.8 \pm 0.6 and 17.2 \pm 1.2 mg/h in the CEI study group. Overall, this represented a 47% reduction in bupivacaine use per hour in patients receiving PCEA for analgesia during the first and second stages of labor.

Table 1. Demographic Data and Labor Characteristics of Patients Receiving Continuous Epidural Infusion Versus Patient-Controlled Epidural Analgesia

Variable	CEI	PCEA	P
Maternal			
Age (yr)	31.5 ± 1.1	32.3 ± 1.2	NS ^a
Height (cm)	160.7 ± 1.2	165.8 ± 1.4	<0.01 ^a
Weight (kg)	77.6 ± 3.0	77.3 ± 3.0	NS ^a
Cervical dilation at time of placement of epidural catheter (cm)	4.3 ± 0.2	4.1 ± 0.3	NS ^a
Duration of labor (h)			
First stage	3.3 ± 0.5	3.8 ± 0.5	NS ^a
Second stage	1.5 ± 0.2	1.3 ± 0.2	NS ^a
Mode of delivery (No.)			
Spontaneous vaginal delivery	13	18	NS ^b
Pitocin augmentation	12	16	NS ^b
Forceps-assisted delivery	4	1	NS ^b
Cesarean delivery	3	1	NS ^b
Episiotomy	13	15	NS ^b
Apgar score ^d			
1 min	8 (5-9)	9 (7-9)	NS ^c
5 min	9 (8-9)	9 (9-10)	NS ^c

CEI, continuous epidural infusion; PCEA, patient-controlled epidural analgesia; NS, not significant. Values are mean ± SEM unless otherwise specified.

^aAnalysis by *t*-test.

^bAnalysis by Fisher's exact test.

^cAnalysis by Mann-Whitney U-test.

^dMedian with range.

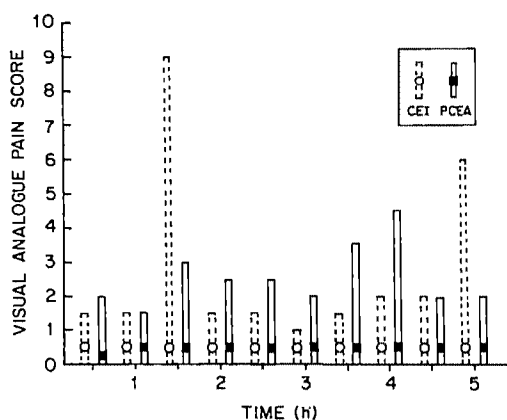


Figure 1. Visual analogue pain scores for patients receiving continuous epidural infusion (CEI) or patient-controlled epidural analgesia (PCEA) after institution of epidural analgesia and subsequent 5 h. Each circle or square (median) with double bars (range) represents 8-20 patients. There is no statistical difference in pain scores over the study period (Friedman χ^2 -test).

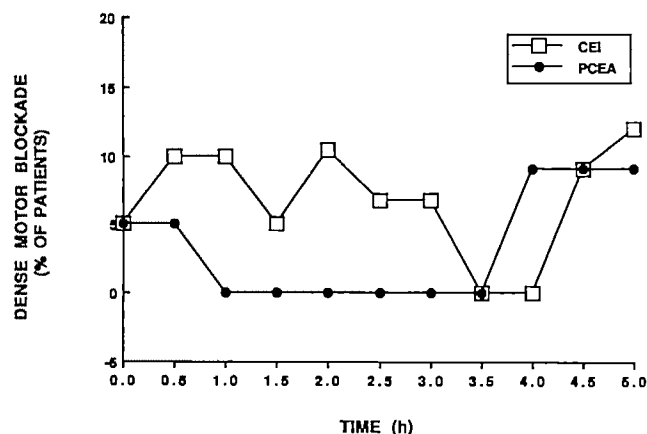


Figure 2. Percentage of patients with dense (grade 2 or 3) motor block after institution of epidural analgesia and subsequent 5 h. There is no statistical difference between the study groups (Friedman χ^2 -test).

Similarly, the total amount of fentanyl used was markedly different between the two study groups (CEI = $112.1 \pm 12.1 \mu\text{g}$; PCEA = $50.8 \pm 7.6 \mu\text{g}$). This represented a dosage reduction of 55% in the PCEA group. When corrected for hourly consumption, the average hourly fentanyl use for the PCEA group in the first and second stages was, respectively, 10.5 ± 1.3 and $8.3 \pm 1.4 \mu\text{g/h}$, as compared with 23.9 ± 0.5 and $23.5 \pm 0.6 \mu\text{g/h}$ in the CEI study group. Overall,

this represented a 56% reduction in the average fentanyl use per hour in patients receiving PCEA.

There were no significant complications resulting from this study. Transient fetal bradycardia developed in one patient in the CEI group, which resolved with repositioning and treatment with oxygen. One newborn from each of the PCEA and CEI groups had fetal meconium aspiration without untoward sequelae. There were no instances of prolonged hypotension or respiratory depression in either study

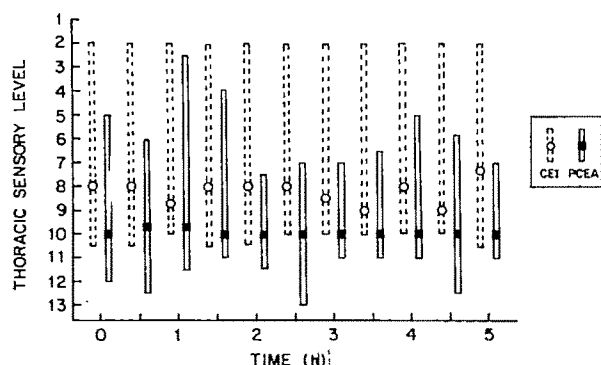


Figure 3. Cephalad extent of sensory blockade (average of bilateral cephalad dermatomes) after institution of epidural analgesia and subsequent 5 h. Each circle or square (median) with double bars (range) represents 8-20 patients. There is no statistical difference between the study groups (Friedman χ^2 -test).

group, but one patient in the CEI group experienced moderate pruritus.

Discussion

We found a 47% decrease in the average hourly dose of bupivacaine required to achieve analgesia using demand-dose PCEA as compared with fixed-rate CEI of the same solution. Despite this decrease, there were no corresponding alterations in the degree of motor blockade or in the extent of sensory anesthesia.

Previous studies comparing CEI with PCEA for analgesia of labor and delivery have used the continuous infusion plus demand-dose mode of PCEA (3,4). Gambling et al. (3), using 0.125% bupivacaine and no fentanyl, demonstrated a 26% decrease in dose with PCEA as compared with fixed-rate CEI, with no corresponding changes in motor or sensory blockade. Lysak et al. (4) used the continuous infusion plus demand-dose mode of PCEA to compare groups receiving: (a) 0.125% bupivacaine, (b) 0.125% bupivacaine with fentanyl (1 $\mu\text{g}/\text{mL}$), and (c) 0.125% bupivacaine, fentanyl (1 $\mu\text{g}/\text{mL}$) and 1:400,000 epinephrine, with physician-controlled CEI using 0.125% bupivacaine. Patient-controlled epidural analgesia with plain bupivacaine had no "dose-sparing" effect. The addition of fentanyl modestly decreased hourly infusion requirements. The authors attributed this to a previously described (5,7) potentiating effect of fentanyl in reducing hourly bupivacaine use.

We may reconcile the results of these three studies by examination of individual study designs.

PCEA Mode

If the literature on patient-controlled analgesia is examined with respect to intravenous opioid admin-

istration in the continuous infusion plus demand-dose mode, there are no strict recommendations as to the optimal rate of background infusion (8-12).

With a ratio of hourly background infusion dose/maximum hourly total dose of 0.25, Owen et al. (10) were unable to demonstrate improved analgesic effectiveness over traditional demand-dose patient-controlled analgesia using intravenous morphine. Furthermore, patients in the continuous infusion plus demand-dose group received on the average more than twice the total dose of morphine of the demand-dose group (73.8 vs 33.9 mg) (10). Sinatra et al. (11) attributed the improved analgesic effect in their continuous infusion plus demand-dose group to a reduction in the background infusion rate (hourly background infusion dose/maximum hourly total dose ratio of 0.07). The total opioid administration was comparable between both modes of patient-controlled analgesia.

According to the protocol of Lysak et al. (4), 30% of the maximum 1-h dose was supplied by the background infusion in the PCEA group. Furthermore, the background infusion rate of the PCEA group was set at approximately 40% of the CEI group's infusion rate.

The results of intravenous dosing with opioids under patient control may not be directly comparable to epidural dosing with local anesthetics. However, the use of the continuous infusion plus demand-dose mode is a hybrid of "pure" patient-controlled analgesia and physician-controlled analgesia. Use of larger background infusion rates places the modality more in the classification of physician-controlled analgesia rather than of patient-controlled analgesia. In the Lysak et al. study, the ratio of hourly background infusion dose/maximum hourly total dose was rather high (0.3). Thus, the study of Lysak et al. may have compared, in actuality, variants of physician-controlled analgesia. This may explain the inability to demonstrate significant dose-sparing effects with PCEA.

Fixed Versus Variable-Rate Continuous Epidural Infusions

Closely supervised analgesia with intramuscular opioids can mimic intravenous patient-controlled analgesia, become on demand, and produce equivalent analgesia (13,14). However, though analgesia may be equivalent, the resultant effects on analgesic requirements remain unsettled (13-15). In the study of Lysak et al. (4), CEI was adjusted hourly in contrast to the fixed rate used in the present study and in that of Gambling et al. (3). Close physician attentiveness and adjustment of infusion rate in the CEI group may

Table 2. Comparison of Epidural Analgesic Requirements During Labor for Continuous Epidural Infusion and for Patient-Controlled Epidural Analgesia*

Variables	Bupivacaine (mg)			Fentanyl (μ g)		
	CEI	PCEA	P	CEI	PCEA	P
Initial bolus						
At time of catheter placement	51.8 \pm 1.7	53.6 \pm 1.4	NS	—	—	—
Subsequent boluses						
First stage	2.6 \pm 1.3	7.9 \pm 2.7	NS	—	—	—
Second stage	3.4 \pm 1.6	2.6 \pm 1.5	NS	—	—	—
Total cumulative use	76.1 \pm 8.5	42.2 \pm 5.9	<0.003	112.1 \pm 12.1	50.8 \pm 7.6	<0.0002
Cumulative hourly usage						
First stage	15.8 \pm 0.6	8.8 \pm 1.1	<0.0002	23.9 \pm 0.5	10.5 \pm 1.3	<0.0002
Second stage	17.2 \pm 1.2	6.8 \pm 1.2	<0.0002	23.5 \pm 0.6	8.3 \pm 1.4	<0.0002
Combined	16.2 \pm 0.8	8.6 \pm 0.9	<0.0002	23.4 \pm 0.6	10.2 \pm 1.0	<0.0002

NS, not significant.

*All analyses by *t*-test, values are mean \pm SEM.

have duplicated the on-demand nature of PCEA. However, the resultant effects on analgesic requirements remain speculative.

In the present study, prompt initiation of CEI after the initial dose of 0.5% bupivacaine could have overestimated the amount of bupivacaine necessary for analgesia in the CEI group. Medication was automatically infused during the 60–90 min of anesthesia attendant with the initial dose of 0.5% bupivacaine. In contrast, the PCEA group controlled the onset of supplemental medication after initial dosing. Similarly, infusion rates less than 12 mL/h could have been used in the CEI group. All these practices are standard for management of CEI at our institution, however.

The CEIs for labor and delivery are set at levels that prevent pain, even when it is most intense; thus, CEIs represent a relative overdose when pain is less severe. Although not statistically significant, the trend toward higher sensory levels, greater motor blockade, and fewer supplemental injections of bupivacaine in the CEI group further suggests the notion of relative overdose. Viewed in this context, it is not entirely surprising that analgesic requirements decrease when the patient is in control.

In summary, a significant dose-sparing effect was seen with the use of demand-dose PCEA as compared with fixed-rate CEI in a randomized, double-blind, placebo-controlled trial for analgesia during labor and delivery. We speculate that the dose-sparing effect was attributable to the use of the demand-dose mode of PCEA, ie, without provision of a background infusion. This reduction in analgesic use was accomplished, however, without improved analgesic efficacy or reduction in degree of motor blockade. However, as the anatomy and physiology of nociception are unique for pain of labor and delivery, we cannot assume that the findings of this

study will generalize to epidural anesthesia/analgesia in other clinical settings.

So far, all studies involving PCEA for labor and delivery have been unable to demonstrate improved analgesic effectiveness as compared with CEI. Improved analgesia with PCEA may need to await determination of the volume-concentration relations of the demand dose and the influence of the duration of the lockout interval with respect to local anesthetics. Although this study suggests that analgesic requirements during labor and delivery may be reduced with demand-dose PCEA, further work is needed to determine the benefit, if any, of various background infusion rates for PCEA with local anesthetics.

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Metoclopramide: An Analgesic Adjunct to Patient-Controlled Analgesia

William H. Rosenblatt, MD, Ann Marie Cioffi, RN, Raymond Sinatra, MD, PhD, Lloyd R. Saberski, MD, and David G. Silverman, MD

Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

This randomized, double-blind trial evaluated the effect of metoclopramide on the pain and analgesic requirements associated with prostaglandin-induced labor for second-trimester termination of pregnancy. After receiving intrauterine prostaglandin, seven women were given intravenous metoclopramide (10 mg), and eight received saline, concurrent with initiation of patient controlled analgesia (PCA). Group differences were assessed with serial visual analogue scale for pain, interval PCA-morphine consumption, and time to fetal delivery. The metoclopramide group used 54% less PCA morphine (24.1 vs

52.0 mg), had lower visual analogue scale scores, and interval morphine consumption at 2, 4, and 6 h after PCA had been initiated, as well as earlier delivery of the fetus when compared with the control group ($P < 0.05$). We conclude that a single dose of metoclopramide reduces the pain and PCA-morphine requirements of patients undergoing prostaglandin-induced labor and may facilitate passage of the fetus. Metoclopramide may have a similar application in treating other types of gynecologic pain.

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Intraamniotic injection of prostaglandin $F_{2\alpha}$ to induce second-trimester abortion results in increased uterine tone with superimposed intermittent contractions (1). Beginning 30-120 min after injection, the patient typically describes a cramping pain similar to that of natural labor but with a more unremitting course (1). As many as 81% of patients undergoing this procedure require analgesic therapy, which traditionally has been provided in the form of parenteral narcotics (2). The abortion usually occurs 5-24 h after injection (3-5).

The following study was undertaken to evaluate metoclopramide as an analgesic adjunct in this setting. Metoclopramide provides analgesia for renal colic and improves analgesia when used for the treatment of narcotic-induced nausea during labor (6,7). This analgesic effect of metoclopramide in the genitourinary tract may be attributed to its antagonism of the dopamine receptor as well as its cholinergic activity, which reduces smooth muscle spasm and increases effective peristaltic action (8).

Methods

The study was approved by the Human Investigation Committee of the Yale-New Haven Medical Center. Informed consent was obtained from 20 adult women, ASA physical status II, who had elected to terminate their second-trimester pregnancies by intraamniotic injection of prostaglandin $F_{2\alpha}$ (Hemabate; Upjohn, 250 μ g). Patients were instructed in the use of a patient controlled analgesia (PCA) device (Abbott Life Care II) and in the use of a visual analogue scale (VAS) for pain (0 = no pain, 10 = worst possible pain). Subjects were randomized to receive either intravenous metoclopramide (10 mg) or an equivalent volume of normal saline solution, when a VAS score greater than 5 was achieved. Patient-controlled analgesia (1 mg of morphine every 6 min on demand and a constant infusion of 1 mg/h) was initiated 10 min after metoclopramide or saline was administered.

Over the next 14 h, at 2-h intervals, the following data were collected: VAS score, interval PCA use and total analgesic usage until discontinuation of PCA, time of fetal and placental abortions, and time of hospital discharge. Differences between the groups in VAS scores were analyzed using the Wilcoxon rank sum test, and differences in morphine consumption by two-factor analysis of variance for repeated measures. Other variables, including demographics,

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Address correspondence to Dr. Rosenblatt, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven, CT 06510.

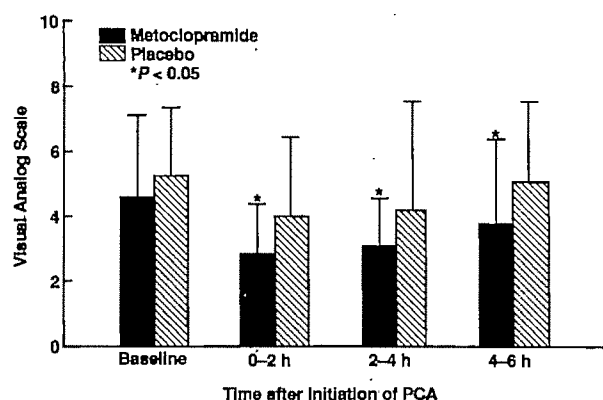


Figure 1. Visual analogue scale scores before and at 2-h intervals after initiating patient-controlled analgesia therapy. Bars represent one standard deviation.

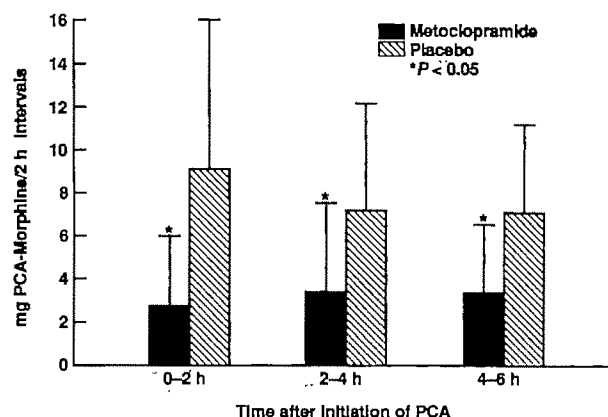


Figure 2. Self-administered morphine dose, presented at 2-h intervals, for the first 6 h of patient-controlled analgesia therapy. Bars represent one standard deviation.

were analyzed using unpaired *t*-test and Fisher's exact test. A *P* value of less than 0.05 was considered statistically significant. Data are presented as mean \pm SD.

Results

Of the 20 patients studied, five were not included in analysis because of incomplete data. Of the remaining subjects, seven received metoclopramide and eight received normal saline solution. The two groups were similar with regard to age, weight, parity, previous gynecologic or other abdominal surgery, gestational age, reason for choosing abortion (e.g., elective, genetic disease), and VAS score before initiating PCA. All patients were alert and responsive during the course of the study.

The metoclopramide group reported significantly lower VAS scores during the first 6 h (Figure 1) ($P < 0.05$). Subsequent to this time there was no further significant difference in VAS scores between groups. The metoclopramide group also used significantly less morphine over the first 6 h (3.1 ± 3.2 vs 7.5 ± 4.4 mg/2 h) (Figure 2) and less total morphine until PCA was discontinued (24.1 ± 15.2 vs 52 ± 12.3 mg) ($P < 0.05$). Analysis of the final 8 h of the study period was hindered by a loss of power, as patients completed the abortion and PCA was discontinued. The lower cumulative total dose of morphine was in part influenced by the fetus being aborted earlier (7.2 ± 3.2 vs 15.3 ± 9.3 h) in the group receiving metoclopramide ($P < 0.05$). No statistically significant differences were found with regard to time of placental abortion or hospital discharge, doses of antiemetic medication (droperidol) administered on demand, or number of prostaglandin E suppositories needed (as dictated by hospital procedural guidelines for delayed onset of uterine contractions).

Discussion

Metoclopramide is a central and peripheral dopamine antagonist with peripheral cholinergic properties. It opposes the gastrointestinal inhibitory effects of the specific dopamine agonist apomorphine and accelerates gastric emptying and intestinal peristalsis (9). Metoclopramide's major clinical uses have included increasing the resting tone of the lower esophageal sphincter, accelerating gastric emptying, reducing postsurgical gastroparesis and postlaparotomy nausea and vomiting, and improving food tolerance in patients with postoperative ileus (9). More recently, metoclopramide has been found to have diagnostic and therapeutic applications in urology (6,10,11).

In the present study, metoclopramide was associated with a significant reduction in the pain associated with induced labor. Furthermore, there was a reduction in the analgesic requirements and accelerated delivery of the abortus. We speculate that the cramping pain of prostaglandin-induced labor may be due to uterine and/or fallopian tube incoordinate muscular contraction (i.e., spasm). As in the gastrointestinal and urinary tracts, metoclopramide may restore normal peristaltic function to this smooth muscle system, thereby reducing the discomfort at its source and providing an improved expulsive force. There is evidence to suggest such a role for dopamine-receptor antagonism in this setting. (a) Dopamine receptors have been identified along the length of the human fallopian tube, and the *in vitro* application of dopamine in the sow oviduct has been shown to depress normal peristaltic activity (8,12). (b) Dopamine antagonism with metoclopramide has been shown to stimulate human ureteral peristalsis and canine detrusor and urethral sphincter activity (10,13). (c) Clinically, metoclopramide is efficacious in the treatment of renal colic (6,11). (d) A previously

reported, incidental finding of Vella et al. was that patients receiving meperidine and metoclopramide (for antiemetic therapy) during spontaneous labor had significantly lower pain scores than those receiving meperidine and promethazine (7).

In our study there were no significant differences in pain scores or analgesic received after 6 h and no difference in the placental delivery time. This may be due to a decline in the plasma level of metoclopramide, which has a half-life of 4-5 h (9,14).

In conclusion, our data indicate that metoclopramide effectively reduces the pain of prostaglandin-induced labor. This was associated with a more rapid delivery of the fetus.

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Prevention of the Cardiovascular and Neuroendocrine Response to Electroconvulsive Therapy: I. Effectiveness of Pretreatment Regimens on Hemodynamics

Matthew B. Weinger, MD, Brian L. Partridge, MD, DPhil, Richard Hauger, MD, and Arvin Mirow, MD

Departments of Anesthesiology and Psychiatry, University of California, San Diego, and Department of Veterans Affairs Medical Center, San Diego, California

Electroconvulsive therapy (ECT) under anesthesia is associated with hypertension and tachycardia. The cardiovascular effects of ECT were studied after pretreatment of 10 patients with esmolol (1.0 mg/kg), fentanyl (1.5 μ g/kg), labetalol (0.3 mg/kg), lidocaine (1.0 mg/kg), and saline solution (control), using a double-blind, randomized block-design. Each patient received all five pretreatment regimens over the course of five ECT sessions. During control studies, arterial blood pressure and heart rate increased significantly in all patients after ECT ($P < 0.05$ and $P < 0.01$, respectively). The rate-pressure product increased by an average of $336\% \pm 14\%$ ($P < 0.01$). There were appreciable individual differences in the cardiovascular response to ECT, independent of pretreatment ($P < 0.01$). Pretreatment with esmolol and

labetalol significantly reduced the hemodynamic response to ECT, compared with fentanyl, lidocaine, or saline solution ($P < 0.05$). Esmolol attenuated arterial blood pressure to a larger extent than did labetalol ($P < 0.05$). Compared with saline solution (control), pretreatment with labetalol, fentanyl, or lidocaine significantly reduced seizure duration ($P < 0.05$) and increased the frequency with which a second electrical stimulus was required. In contrast, esmolol pretreatment did not significantly affect seizure duration. Esmolol (1 mg/kg), administered 1 min before induction of anesthesia, produced significant amelioration of the cardiovascular response to ECT with minimal effect on seizure duration.

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Electroconvulsive therapy (ECT) is frequently used for patients with major affective disorders. However, ECT may be associated with significant cardiovascular morbidity and mortality (1-3). For example, 35 cardiac arrests during ECT were reported in California from 1974 through 1983 (2), and cardiovascular mortality has been reported to be as high as 0.03% (3). The cardiac morbidity of ECT is usually due to arrhythmias and lability of arterial blood pressure (BP) resulting in myocardial infarction, congestive heart failure, cardiac arrest, and/or cerebrovascular accidents. The hemodynamic lability probably results from sympathetic and parasympa-

thetic outpouring after the administration of the electric shock and the resultant seizure. Electroconvulsive therapy is a strong stimulus for sympathetic and adrenomedullary catecholamine release. Three-fold to 15-fold increases in serum levels of norepinephrine and epinephrine after ECT were demonstrated in the study of Gravenstein et al. (4).

A number of drug regimens have been suggested to prevent or to ameliorate the hemodynamic response to ECT. Recommended pretreatment regimens to block the ECT-induced hypertensive response include trimethaphan (5), sodium nitroprusside (6,7), Diazoxide (8), hydralazine (7), nitroglycerin (3), esmolol (9,10), and labetalol (11). Similarly, prevention of ECT-induced arrhythmias has been attempted with pretreatment using lidocaine (12,13) and propranolol (14-16). The new β -adrenoceptor antagonists esmolol and labetalol have not been systematically investigated for the latter purpose.

Unfortunately, the administration of adjuvant cardiovascular drugs may shorten seizure duration, thereby potentially diminishing the therapeutic effec-

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Address correspondence to Dr. Weinger, VA Medical Center (125), 3350 La Jolla Village Drive, San Diego, CA 92161.

tiveness of ECT. Seizures lasting less than 20 s are generally without therapeutic benefit (17). Seizure duration is reduced by barbiturates (18), propofol (19), lidocaine (20), and diazepam (21). The effect of β -adrenergic blockers such as propranolol (14,15) and esmolol (9,10,22) on seizure duration is controversial.

Thus, although it is desirable to prevent the cardiovascular responses to ECT, the proper choice of a premedication to accomplish this remains unclear. The purpose of this study was to rigorously compare four previously advocated pretreatment regimens (esmolol, fentanyl, labetalol, and lidocaine) with respect to their effects on cardiovascular hemodynamics and seizure duration during ECT, using a double-blind, randomized, placebo-controlled, crossover design. The neuroendocrine (catecholamines, ACTH, cortisol, and vasopressin) responses to ECT were also examined (23).

Methods

After obtaining Human Subjects Committee approval and patients' informed consent, 10 patients were studied during five sequential ECT treatments administered on a three times per week schedule. Electroconvulsive therapy treatments were performed in the postanesthesia care unit at the San Diego VA Medical Center.

All patients received their usual chronic medications (such as antidepressants) in the morning before each ECT session. No patient was receiving chronic antihypertensive therapy at the time of hospital admission or during the study. Patients were brought to the postanesthesia care unit where they were monitored with a precordial stethoscope and pulse oximeter. In addition, continuous records were made of arterial BP (both by Finapres continuous finger BP and by Dynamap BP), five-lead electrocardiogram (ECG), instantaneous heart rate (HR), and electroencephalogram (EEG) (one channel, midline forehead to right mastoid). An intravenous catheter was inserted, and adequate intravascular volume status was assessed clinically. Tilt tests were used as needed to confirm normovolemia. After baseline BP and HR measurements were made, patients breathed oxygen through a mask for 5 min.

Each patient then received intravenous injection of two coded syringes (A and B) before induction of anesthesia. Both syringes were prepared in advance by an individual not involved in the study. One of the two syringes always contained only saline solution; the other, a study drug. This was done to maintain blinding of the study solutions despite the longer onset times of labetalol and fentanyl. Thus, fentanyl (1.5 μ g/kg) and labetalol (0.3 mg/kg) were administered 5 min before induction of anesthesia, whereas

esmolol (1 mg/kg) and lidocaine (1 mg/kg) were administered 1 min before induction. Doses of the study drugs were chosen based on the literature (9-12) and on previous clinical experience.

Using a cross-over design, each patient received each study drug on a single occasion for a total of four treatment sessions. In addition, each subject also underwent a fifth (control) study in which two saline placebo injections were used. The order of the treatments was determined by a random table prepared before the study of the first patient. Drugs were drawn up fresh in normal saline solution to achieve a total volume of 10 mL. All persons present at the ECT session were blinded to the identity of the study drugs. The BP, HR, and EEG tracings were analyzed later by an individual who was also blinded to treatment regimens.

Each patient received one to three ECT treatments before entering the study. This allowed determination of the most appropriate doses of methohexital and succinylcholine for anesthetic induction as these doses vary between patients (3). Once doses of methohexital and succinylcholine sufficient to produce anesthesia and paralysis without prolonged awakening time had been chosen, these doses were used throughout the study. Methohexital and succinylcholine doses in this study ranged from 0.8 to 1.5 mg/kg (1.2 ± 0.06 mg/kg, mean \pm SEM) and from 0.56 to 1.0 mg/kg (1.04 ± 0.06 mg/kg), respectively (Table 1).

Five minutes after administration of the first syringe (A) and 1 min after administration of the second syringe (B), anesthesia was induced with the preestablished dose of methohexital. When the patient became unresponsive, ventilation was assisted by mask; and an arterial BP cuff was inflated to 300 mm/Hg on one calf to isolate the limb (24). The patient then received succinylcholine; and after fasciculations occurred, a mouth guard was inserted. The patient's lungs were hyperventilated for 30 s (25). Unilateral ECT was then performed using a Thymatron ECT machine (Somatics, Inc.). The ECT machine settings (charge 504 mC, current 0.9 A, frequency 70 Hz, pulsewidth 1.00 ms, and duration 4 s) were not adjusted during the study. If no seizure occurred after the stimulus, a second (and on one occasion a third) stimulus was administered 2 min later.

Systolic, diastolic, and mean BPs, HR, seizure duration (both EEG and observed isolated limb), and time from anesthetic induction to spontaneous ventilation and awakening (response to verbal commands) were recorded. In addition, for each ECT treatment, rate-pressure product (RPP) was calculated.

Except where noted, data were analyzed by two-way repeated measures analysis of variance, with significant interactions investigated by Neumann-

Table 1. Patient Characteristics

Patient	Age (yr)	Weight (kg)	Medical history	Methohexital (mg/kg)	Succinylcholine (mg/kg)	Time to awakening (s)	Mean starting SBP (mm Hg)	Mean starting HR (beats/min)	Mean increase in SBP (mm Hg)	Mean increase in HR (beats/min)
1	57	60	COPD	1.3	1.1	447	167	65	31	23
2	63	85	CAD/ HTN	0.82	0.98	370	131	73	85	66
3	74	90	CAD/ HTN	1.3	1	302	152	68	74	36
4	59	68	None	1.2	0.88	221	141	86	50	33
5	43	62	None	1.1	0.96	331	123	54	46	41
6	28	100	None	1.3	0.68	258	95	66	16	24
7	74	71	None	1.1	1.4	342	151	70	80	35
8	47	73	None	1.4	1.1	432	116	48	20	20
9	64	66	None	1.5	1.2	304	150	78	38	53
10	45	81	None	1	1.1	406	131	57	3	20
Mean	55.40	75.60		1.20	1.04	341.30	135.70	66.50	44.30	35.10
SEM	4.63	4.12		0.06	0.06	23.32	6.64	3.59	8.93	4.77

COPD, chronic obstructive airway disease; CAD, coronary artery disease; HTN, hypertension.

Keuls tests (26). $P < 0.05$ was considered significant. Data are presented as mean \pm SEM.

Results

Control Studies

Patient characteristics are presented in Table 1. Patients differed significantly in their preanesthetic BP and HR values ($P < 0.001$). However, all initial (control) BP and HR values were within the normal range. Therefore, all subsequent BP and HR values were expressed as percentage of control BP or HR rather than absolute values.

During control studies, ECT significantly increased arterial BP and HR in every patient. Transient increases in systolic BP to as high as 313 mm Hg were recorded. The rate-pressure product immediately after seizure increased by $336\% \pm 14\%$ ($P < 0.01$). In addition, a large number of ECG abnormalities were seen, including ventricular arrhythmias, ST segment changes, and sinus pauses (lasting up to 4 s). Patients differed in their propensity to respond to ECT with ECG changes. Within the next few minutes, BP and HR decreased to near control levels and ECG normalized. However, on emergence from anesthesia, BP but not HR increased again, sometimes to values larger than those seen immediately after ECT (Figure 1). At this time, RPP increased to an average of $223\% \pm 24\%$ above control ($P < 0.01$).

Seizure duration, as measured by EEG, correlated well with that observed for isolated limb myoclonic activity (Figure 2). In general, the electrical manifestations of the seizure were present for 5–8 s longer than limb movement. Treatment groups were not

significantly different. The EEG was used as the dependent variable for seizure duration in subsequent analyses.

Interindividual Variation

Hemodynamic response to ECT, reflected by increased systolic BP or HR varied considerably between patients ($P < 0.001$), with mean increases in BP of $155\% \pm 3\%$ ($P < 0.05$ compared with baseline) and in HR of $164\% \pm 9\%$ ($P < 0.01$). There were no differences in the HR or BP response to ECT associated with the order of drug treatment. There were significant interpatient differences in the time from induction of anesthesia to awakening ($P < 0.05$), although this was not related to methohexital dose (Table 1). Patients differed significantly in seizure duration ($P < 0.01$) and in awakening time. As described by Sackeim et al. (27), the seizure elicited during the first ECT session (55 ± 13 s) was significantly longer in duration than the seizures during the last two ECT sessions (32 ± 3 s, $P < 0.05$, Fisher least significant difference procedure).

Effectiveness of Pretreatment Drugs

There were no differences between treatment groups in initial BP, HR, or in time to awakening (Table 2). Significant differences were noted, however, in systolic and mean BPs, HR, and RPP between the five premedication regimens ($P < 0.01$). There were significantly smaller increases in systolic BP after esmolol pretreatment than after fentanyl or saline pretreatment ($P < 0.05$) (Figure 3). Both esmolol and

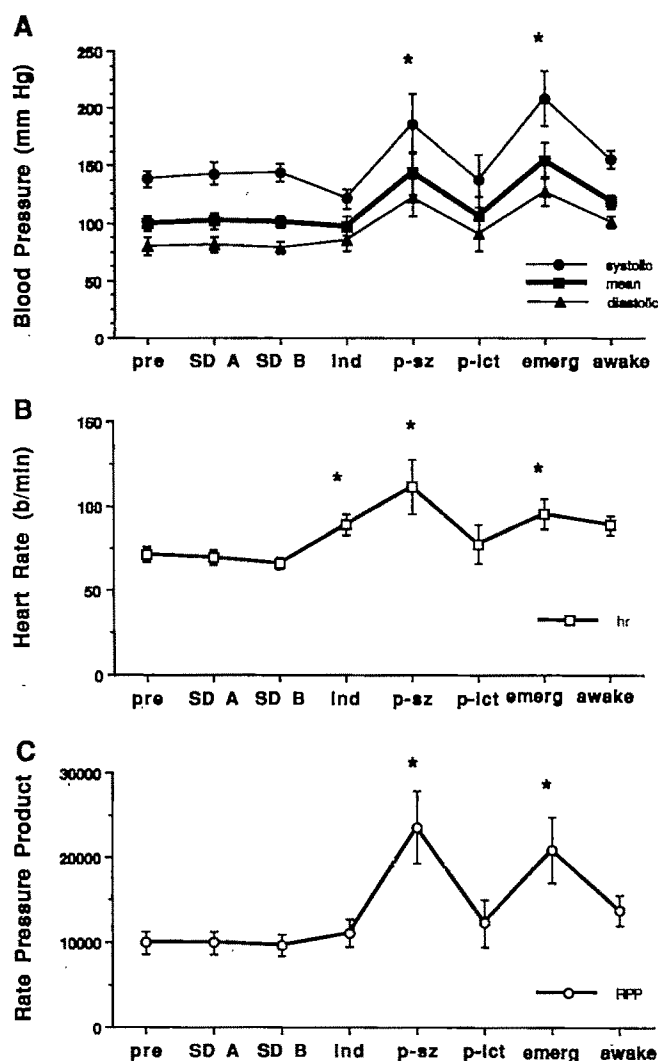


Figure 1. Unmodified responses to ECT. Shown are the average responses of 10 patients receiving saline control (SD A and SD B) pretreatments. **A** shows the response of arterial blood pressure (mean \pm SEM), **B** shows the heart rate response, and **C** shows the rate-pressure product. Significant increases, indicated by asterisks, were seen both at the time of the seizure (p-sz) and during emergence from anesthesia. In addition, heart rate increased significantly immediately after induction of anesthesia (ind). p-ict = post ictal.

labetalol significantly attenuated, to an equivalent degree, the tachycardia seen after saline, fentanyl, or lidocaine pretreatments ($P < 0.01$). Similarly, the increase in RPP after ECT was significantly diminished by both labetalol and esmolol compared with fentanyl, saline solution, or lidocaine ($P < 0.01$).

The hemodynamic response on awakening was similarly attenuated by the different pretreatment regimens in a manner similar to their effect after seizure. Esomolol's effectiveness was, however, less pronounced, and the HR response in esmolol-pretreated individuals was not different from that of

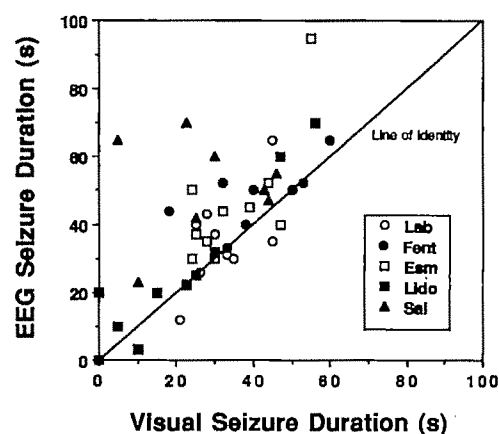


Figure 2. Seizure duration after drug pretreatments. Seizure duration as measured by single-channel EEG and as visualized by the isolated limb technique. Shown are responses for each of the four drug pretreatments (labetalol [Lab], fentanyl [Fent], esmolol [Esm], and lidocaine [Lido]) and saline (Sal). The seizure as measured by EEG was usually 5-8 s longer than that measured by observation of the isolated limb.

control patients. This was consistent with the finding that HR did not increase significantly in control patients during emergence.

When seizure duration was examined as a function of drug pretreatment, there was a significant treatment effect ($P < 0.05$). Compared with saline solution, labetalol, lidocaine, and fentanyl significantly decreased seizure duration whereas esmolol had no significant effect (Table 3). Compared with either fentanyl or labetalol, lidocaine resulted in significantly shorter duration of seizures ($P < 0.05$). Six of 10 patients pretreated with lidocaine required additional electrical shocks to induce a seizure, whereas in patients pretreated with esmolol and with labetalol or fentanyl only one and two, respectively, required additional electrical shocks ($P < 0.05$, χ^2 test).

Discussion

This double-blind, randomized, placebo-controlled study demonstrates that the new β -adrenergic blockers labetalol and esmolol significantly attenuate the cardiovascular response to ECT. In contrast, at the doses studied, neither lidocaine nor fentanyl pretreatment had comparable ameliorating effects. In addition, esmolol did not significantly shorten seizure duration, whereas the other three pretreatment regimens did adversely affect the therapeutic benefit of ECT.

The elicitation of a seizure is classically thought to produce an intense parasympathetic discharge that can result in transient bradycardia or even asystole (3,4). During the present study, there was one clinically significant episode of sinus arrest out of 50

Table 2. Treatment Groups

Treatment	n	Time to awakening (min)	Heart rate		Systolic blood pressure		Rate-pressure product	
			Starting (beats/min)	After seizure (beats/min)	Starting (mm Hg)	After seizure (mm Hg)	Starting	After seizure
Labetalol	10	318 ± 28	65 ± 3	85 ± 6	134 ± 7	179 ± 15	8,026 ± 626	15,719 ± 1,905
Fentanyl	10	330 ± 70	68 ± 4	116 ± 8	130 ± 9	183 ± 14	8,914 ± 747	21,706 ± 2,565
Esmolol	10	339 ± 39	67 ± 5	97 ± 7	142 ± 10	175 ± 11	9,769 ± 1327	17,369 ± 2,092
Lidocaine	10	347 ± 47	65 ± 4	99 ± 9	135 ± 9	187 ± 16	8,832 ± 862	17,924 ± 3,095
Saline solution	10	372 ± 29	71 ± 4	117 ± 2	136 ± 7	196 ± 13	9,749 ± 818	23,561 ± 2,843

Values are mean ± SEM.

treatments examined. Others have recommended routine administration of anticholinergic drugs (28–30) before induction of anesthesia. In contrast to Kovak et al. (9), vagolytic premedication was not used in the present study because it would have made interpretation of the data more difficult.

After the circumscribed period of primarily vagal activity, which does not always occur, sympathoadrenal tachycardia occurs. This is thought to arise initially from direct adrenergic outflow through paravertebral sympathetic ganglia but is sustained by catecholamines released from the adrenal medulla (4,31). Marked tachycardia is frequently associated with ECG abnormalities, most commonly premature ventricular beats (28) and transient T-wave alterations (32,33). Although the incidence of T-wave changes is higher in patients with preexisting cardiac disease (31), it is controversial whether this represents cardiac ischemia (32,33).

We have observed systolic BP larger than 300 mm Hg in patients receiving ECT. The present data are consistent with previous studies showing that systolic hypertension was more pronounced than diastolic hypertension after ECT (34). In the patients studied, a secondary hypertensive response was observed at the time of emergence. This second increase in BP has not been reported previously, possibly because close monitoring of patients has been discontinued at the time of emergence.

A number of premedications have been proposed to blunt the hemodynamic response to ECT (5–11). However, it has been difficult to evaluate the relative efficacy of these techniques as most appear in the literature as case reports. In addition, although some studies have compared pretreatment agents with control treatment, no previous study has compared several different pretreatment agents with each other (5,7,9–11).

This study was designed to compare single "best" doses of individual drugs. The drug doses studied were chosen based both on previous studies (9–12) and on our past clinical experience. The intent was to choose one dose of each drug that would have a

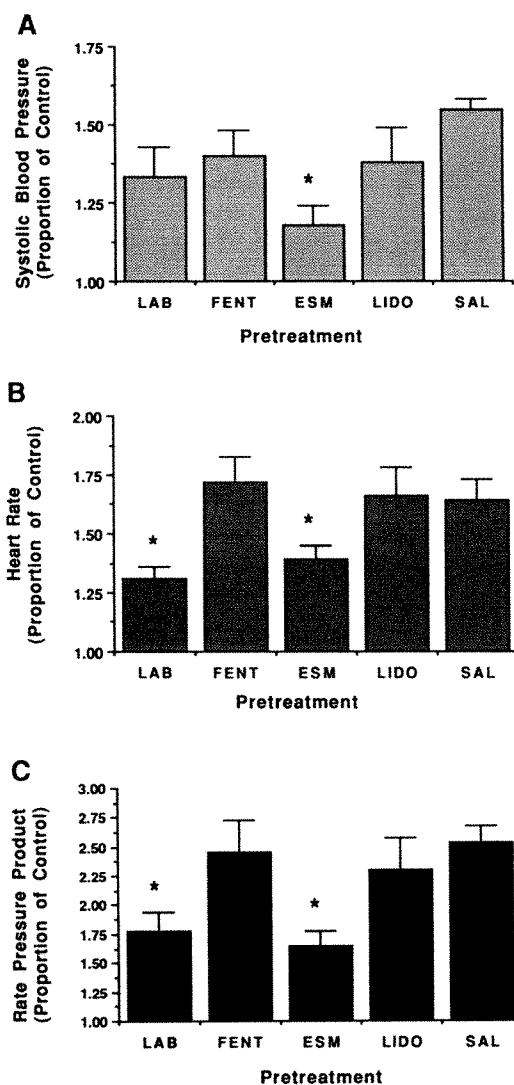


Figure 3. Effect of drug pretreatments on systolic blood pressure (A), heart rate (B), and rate-pressure product (C). Shown are mean maximum values during the seizure as a proportion of control (preoperative) values calculated individually for each patient and then averaged. Values for labetalol (LAB), fentanyl (FENT), esmolol (ESM), lidocaine (LIDO), and saline (SAL) are shown. An asterisk indicates significance ($P < 0.05$) compared with preoperative values. Esmolol significantly ameliorated the blood pressure response to ECT. Both labetalol and esmolol significantly attenuated the HR response and the rate-pressure product.

Table 3. Effect of Pretreatment on Seizure Length

Treatment	Seizure duration (s)	No. requiring second stimulus	No. of inadequate seizures
Labetalol	36.9 ± 4.5 ^a	2	1
Fentanyl	43.6 ± 4.1 ^a	2	0
Esmolol	45.8 ± 5.9	1	0
Lidocaine	26.5 ± 7.2 ^a	6	3
Saline solution	56.5 ± 12.5	0	0

^aSignificantly different from control values ($P < 0.05$).

recognizable effect, would not result in significant cardiovascular depression before ECT, and would not delay awakening after ECT. These goals appeared to be met with the doses tested. No drug significantly altered pre-ECT hemodynamics or post-ECT awakening times. Esmolol and labetalol, but not lidocaine or fentanyl, significantly ameliorated the cardiovascular responses to ECT. Nevertheless, different doses may have produced slightly different results and complete dose-response curves for each drug would have permitted more definitive conclusions.

In this study, in contrast to the effects of the other pretreatment agents, esmolol did not significantly shorten seizure duration. In one previous study in which patients were tested repeatedly, esmolol appeared to decrease seizure duration (10); whereas in another study, no effect was seen (9). However, in both studies, considerably larger doses of esmolol were used. It is possible that, in the present study, a larger patient sample size would have demonstrated a significant reduction in seizure duration. Esmolol appears to have general anesthetic properties (35), and this would presumably affect seizure duration if a sufficient dose were given. However, in a study that used a larger dose of esmolol (10), seizure duration was only modestly reduced and did not jeopardize the therapeutic efficacy of ECT.

Any study measuring the seizure duration after ECT should control for the possible effects of drug-induced respiratory depression as hypercarbia decreases seizure duration (25). In the present study, all patients were hyperventilated before the ECT shock. Of the drugs tested, fentanyl might have been expected to produce the greatest degree of ventilatory depression and, thereby, should have decreased seizure duration the most. Yet, this was not the case. On the other hand, lidocaine, at the dose studied, produced the greatest reduction in seizure duration, a result consistent with previous studies (14,20). Labetalol also significantly reduced seizure duration. Smaller doses of labetalol might have had less effect on seizure duration but may not have produced equivalent blunting of the cardiovascular response.

Esmolol has a rapid onset and short duration, is

readily available on most anesthesia carts, and reliably blunts the cardiovascular response to the initial seizure. Thus, when unacceptable cardiovascular responses to ECT occur, a single bolus of esmolol should rapidly control BP and HR. One previous study (9) used a bolus of esmolol followed by a continuous infusion and another used an infusion alone (10), but this approach may be unnecessarily complex for what is a very brief period of patient risk.

In conclusion, esmolol (1.0 mg/kg) administered 1 min before induction of anesthesia for ECT significantly reduced the cardiovascular response to a greater extent than did fentanyl, lidocaine, or saline control without adversely affecting seizure duration. Although labetalol (0.3 mg/kg given 5 min before induction) also significantly blunted the cardiovascular response to ECT, seizure duration was reduced.

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Prevention of the Cardiovascular and Neuroendocrine Response to Electroconvulsive Therapy: II. Effects of Pretreatment Regimens on Catecholamines, ACTH, Vasopressin, and Cortisol

Matthew B. Weinger, MD, Brian L. Partridge, MD, DPhil, Richard Hauger, MD, Arvin Mirow, MD, and Marvin Brown, MD

Departments of Anesthesiology, Psychiatry, and Medicine, University of California, San Diego, and Department of Veterans Affairs Medical Center, San Diego, California

The neuroendocrine response to electroconvulsive therapy (ECT) was assessed in four patients after pretreatment with esmolol (1.0 mg/kg), fentanyl (1.5 μ g/kg), labetalol (0.3 mg/kg), and saline solution (control). Each patient received each drug pretreatment using a double-blind, randomized study block-design. During each of the five studies, blood samples were obtained from each patient before anesthetic induction, before ECT shock, and at 1, 5, 10, and 30 min after seizure. Samples were subsequently analyzed for epinephrine, norepinephrine, adrenocorticotrophic hormone (ACTH), arginine vasopressin (AVP), and cortisol. Electroconvulsive therapy after saline pretreatment resulted in a 3-fold and 15-fold increase in norepinephrine and epinephrine levels, respectively ($P < 0.05$). The ACTH and cortisol levels gradually increased over 30 min, peak-

ing at values that were two to three times the control values ($P < 0.05$). The AVP levels increased significantly after induction of ECT ($P < 0.005$) and remained higher than control levels at 5, 10, and 30 min. The effect of pretreatments varied. Pretreatment with esmolol and fentanyl resulted in significant attenuation of the norepinephrine peak after seizure ($P < 0.05$). Only esmolol significantly attenuated ECT-induced epinephrine secretion, whereas fentanyl pretreatment significantly reduced release of ACTH after ECT. No pretreatment significantly affected the elevated AVP or cortisol levels seen on emergence or up to 30 min after treatment. The ability of esmolol pretreatment to attenuate serum catecholamine release after ECT is consistent with its ability to block the cardiovascular responses to ECT.

(Anesth Analg 1991;73:563-9)

Electroconvulsive therapy (ECT) is a frequently used therapy for patients with major affective disorders but may have significant cardiovascular morbidity (1). In our accompanying paper (2), it was demonstrated that esmolol and labetalol significantly attenuated the cardiovascular response to ECT. The mechanism by which ECT produces tachycardia and hypertension remains to be fully elucidated. Previous studies have measured catecholamine (3,4) and stress hormone (5) release after ECT. However, the effect on neuroendocrine release of

administering pretreatment drugs to blunt the cardiovascular response to ECT has not been examined.

The purpose of this study was to compare, using a double-blind, randomized, placebo-controlled, cross-over design, three previously advocated pretreatment regimens (esmolol, fentanyl, and labetalol) with saline controls with respect to their effects on serum catecholamines (epinephrine and norepinephrine) and on three markers of the stress response (adrenocorticotrophic hormone [ACTH], arginine vasopressin [AVP], and cortisol) and to correlate these neuroendocrine effects with the hemodynamic response to ECT.

Methods

After Human Subjects Committee approval and patients' informed consent had been obtained and simultaneously with part I of this study (2), five of the

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Address correspondence to Dr. Weinger, VA Medical Center (125), 3350 La Jolla Village Drive, San Diego, CA 92161.

Table 1. Medications Before Electroconvulsive Therapy

Patient No.	Age (yr)	Chronic medications
1	47	None
2	74	Synthroid
3	59	Digoxin, Coumadin, Isordil
4	43	Imipramine
5	28*	Amantadine, Haloperidol

*Because of technical difficulties in sample collection, this patient's data was excluded from analysis.

10 patients in that study had blood drawn during their ECT sessions for measurement of serum catecholamines and stress hormones. They were studied during sequential ECT treatments administered on a three times per week schedule. The ECT treatments were performed in the postanesthesia care unit at the San Diego VA Medical Center.

All patients received their usual chronic medications in the morning before ECT therapy (Table 1). No patient was receiving chronic antihypertensive therapy at the time of hospital admission or during the study.

Patients were brought to the PACU where they were monitored with a precordial stethoscope and pulse oximeter. In addition, continuous records were made of arterial blood pressure (BP) (both by Finapres continuous finger BP and by Dynamap BP), five-lead electrocardiogram (ECG), instantaneous heart rate (HR), and electroencephalogram (EEG) (one channel, midline forehead to right mastoid). An intravenous catheter was inserted in each arm (one for drug infusion and one for blood drawing), and adequate volume status was assured clinically. Tilt tests were used as needed to confirm normovolemia. After baseline BP and HR measurements were made, patients received oxygen through a mask for 5 min.

The method for blinding the experimental treatments and the general methods for the study are described in detail in part I of this study (2). Simultaneously with BP and HR measurements described previously (2), serum was drawn for catecholamine and hormone assays in a subset of the 10 patients. Cost constraints limited this part of the study to five patients. Ideally, assays would have been made for each of the five study pretreatments described in (2). Because of ethical constraints on the total amount of blood that could be sampled from individual patients, however, serum samples were obtained for only four of the treatments: control, labetalol, esmolol, and fentanyl. The following mechanism was used to maintain the blinding of the study personnel: control (saline solution) samples were obtained during the last of the prestudy trials in part I (2). Blood samples were then drawn during three of the five study trials,

when the unblinded pharmacist who was preparing the study drugs determined that esmolol, labetalol, or fentanyl were being administered. Thus, participants did not know which of three study drugs were being administered on the days blood samples were drawn and did not know which of two treatments were being given on the days when samples were not drawn. Additionally, the persons analyzing blood samples, BP, HR, and EEG tracings were blinded to the study drugs administered (2).

Blood samples were collected before anesthesia, after administration of study drugs and induction of anesthesia, and at 1, 5, 10, and 30 min after seizure. Samples were stored in ice. Plasma levels of epinephrine, norepinephrine, ACTH, AVP, and cortisol were measured for each time period.

Ten milliliters of whole blood was collected for pituitary-adrenal hormone assays in glass Vacutainer tubes containing edetic acid that had been chilled on ice. An additional 5-mL blood sample was collected for catecholamines in ice-cold polypropylene tubes containing ethylene glycol tetraacetic acid and glutathione. Within 30 min of collection, all samples were centrifuged at 3000 g (4°C) for 20 min. Aliquots of the separated plasma were stored in polypropylene tubes at -80°C until assayed.

Pituitary-Adrenal Hormone Assays

ACTH immunoradiometric assay. Plasma ACTH concentrations were measured using a highly sensitive immunoradiometric assay (IRMA) developed at the Nichols Institute (San Juan Capistrano, Calif.) (6,7). This assay uses two antibodies with high affinity and specificity for defined regions of the ACTH molecule. The monoclonal antibody (Ab(m)), which binds only to the N-terminal region of ACTH, was radiolabeled with ¹²⁵I for detection. The polyclonal antibody (Ab(p)), which binds only to the C-terminal region of ACTH, is coupled to biotin. The sandwich complex is completed by the addition of an avidin-coated plastic bead.

After a 20-h incubation, aspiration followed by multiple washings of the bead complex resulted in the removal of all unbound components from the standards, controls, and subject samples. The remaining radioactivity is directly proportional to the amount of intact ACTH in the sample. A computer-assisted four-parameter logistics data reduction program compares the radioactivity in the samples with the dose-response curve and computes the ACTH concentration.

The highest ACTH concentration measurable without dilution is approximately 1700 pg/mL, whereas the detection limit (assay sensitivity) is 1.0 pg/mL. The intraassay and interassay variances

are approximately 3% and 7%, respectively. When added to the zero standard, the ACTH IRMA was found to possess no crossreactivity with the ACTH fragments ACTH₁₋₁₀, ACTH₁₁₋₂₄, and ACTH₁₈₋₃₉, α - and β -melanocyte stimulating hormone, β -lipotropin stimulating hormone, or β -endorphin.

Cortisol radioimmunoassay. Plasma cortisol concentrations were measured by standard double-antibody radioimmunoassay (RIA) (Diagnostic Products, Los Angeles, Calif.) using the method of Roller et al. (8). The intraassay and interassay coefficients of variation are 4% and 6%, respectively. The standard range is 0.3–50 μ g/dL with an assay sensitivity of 0.3 μ g/dL.

Vasopressin radioimmunoassay. Circulating levels of vasopressin were measured with a specific RIA after vasopressin was extracted from plasma using an amberlite cation exchange method (9,10). The vasopressin antiserum was kindly provided by Dr. J. Fernstrom (Western Psychiatric Institute and Clinic, Pittsburgh, Pa.) and Dr. L. Fisher (University of Arizona Health Sciences Center, Tucson, Ariz.). ¹²⁵I-Vasopressin was obtained from Dupont-NEN (Boston, Mass.). The minimal level of detection is 0.25 pg/tube and the intraassay coefficient of variation is 3%.

Catecholamine assays. Plasma concentrations of norepinephrine and epinephrine were measured using the single isotope radioenzymatic method of Peuler and Johnson (11), with modifications previously described (12).

Data analysis. Data were analyzed by two-way repeated-measures analysis of variance with significant interactions investigated by Neumann-Keuls tests (13). $P < 0.05$ was considered significant. Data are presented as mean \pm SEM.

Results

Because of technical difficulties, complete serum samples could only be obtained from four of the five patients. In the middle of one ECT study, the intravenous catheter became dysfunctional, precluding blood sampling in one patient. Because of the within-subjects study design, this patient had to be excluded from the data analysis.

Norepinephrine and Epinephrine

Baseline levels of norepinephrine and epinephrine were not significantly different before or after induction of anesthesia and administration of study drugs

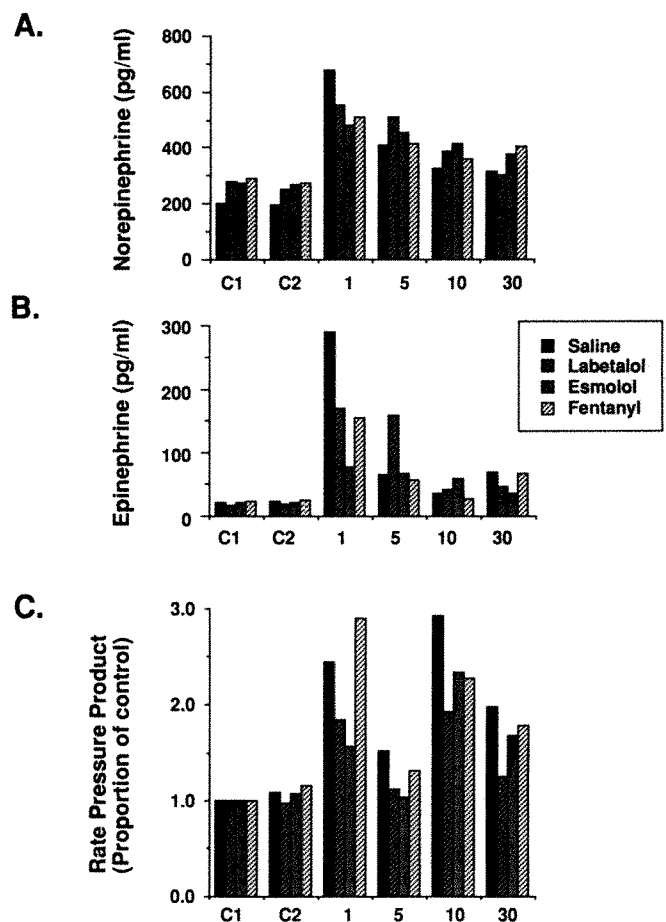


Figure 1. Catecholamine response to ECT. Shown are mean values for four patients pretreated with labetalol, esmolol, fentanyl, or saline solution. The figure shows plasma levels of norepinephrine (A), plasma epinephrine (B), and the rate-pressure product (C) at the equivalent time periods for the four patients included in this analysis (see Reference [2] for complete description of hemodynamics after ECT). Blood samples were drawn preoperatively (C1), after pretreatment and induction of anesthesia (C2), and at periods 1, 5, 10, and 30 min after ECT. Both esmolol and fentanyl significantly attenuated the increase in norepinephrine levels seen at 1 min ($P < 0.05$), whereas esmolol alone significantly attenuated the epinephrine response at 1 min ($P < 0.05$). See text for details.

(Figure 1). Neither were baseline values different between study drugs or between study drugs and control. In all study groups, there were significant increases in serum norepinephrine and epinephrine at 1 and 5 min after seizure, with 3-fold and 15-fold increases exhibited during ECT, respectively (Figure 1A,B). In addition, even with the small sample size, significant differences in the ECT-induced increases in norepinephrine levels at 1 min after seizure were observed. The norepinephrine response after saline pretreatment was significantly greater than that after either esmolol or fentanyl pretreatment ($P < 0.05$), whereas pretreatment with labetalol did not significantly affect the norepinephrine response. The nor-

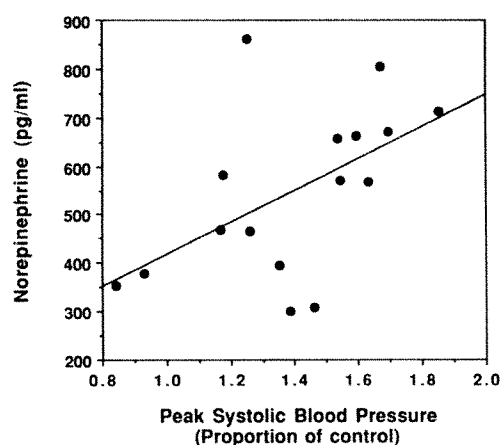


Figure 2. Correlation of norepinephrine with maximal systolic BP. Shown is a correlation plot between plasma norepinephrine (y-axis) and the maximal systolic BP attained after ECT (x-axis). Maximal systolic BP correlated loosely but significantly with plasma norepinephrine ($r = 0.52$, $P < 0.05$) but did not correlate with plasma epinephrine.

epinephrine responses to ECT at 5, 10, and 30 min were not significantly different.

Electroconvulsive therapy also resulted in significant increases in plasma epinephrine at 1 min (Figure 1B, $P < 0.05$) with return to control levels by 5 min after ECT. Esmolol pretreatment resulted in significantly lower levels of epinephrine at 1 min compared with saline ($P < 0.05$). No other significant differences were observed. Hemodynamic responses of the four individuals in this study did not differ significantly from those of the other six patients described in part I (2) (Figure 1C).

Plasma norepinephrine but not epinephrine correlated loosely with the maximum systolic BP achieved after ECT (Figure 2, $r = 0.52$, $P < 0.05$). Neither norepinephrine nor epinephrine levels were significantly correlated with HR after seizure. In addition, no correlation was demonstrated between the serum levels of norepinephrine or epinephrine and either BP or HR at the time of emergence.

ACTH and Cortisol

Baseline levels of ACTH and cortisol did not differ between groups. Furthermore, the plasma ACTH concentrations were not altered by the administration of study drugs and by the induction of anesthesia. Performance of ECT resulted in a mean increase in ACTH level from 42.3 ± 9 pg/mL to 182.1 ± 23 pg/mL. In addition, labetalol and fentanyl treatments significantly reduced the ACTH response at 1, 5, and 10 min after ECT ($P < 0.05$, Figure 3A). The effect of fentanyl was greatest, with significant ($P < 0.05$) differences between ACTH levels seen at 5 and

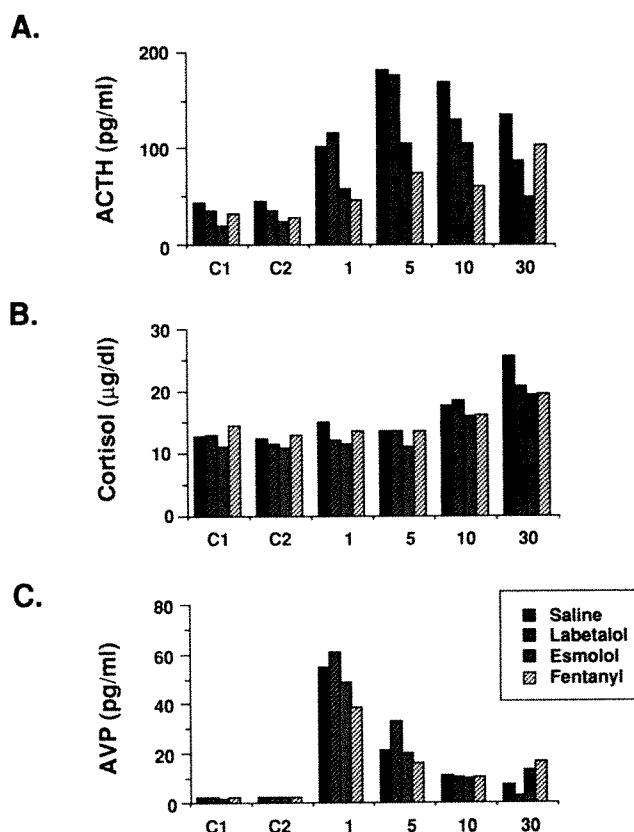


Figure 3. Neuroendocrine response to ECT. Shown are mean values for ACTH (A), cortisol (B), and AVP (C) for the same four patients as in Figure 1. Significant increases in ACTH and AVP are seen at all time periods after 5 min. There was a significant correlation between ACTH levels at 5 min and cortisol levels at 30 min ($P < 0.05$). Fentanyl significantly reduced the increase in ACTH, compared with the labetalol group at 1, 5, and 10 min and compared with saline solution and esmolol at 5 and 10 min ($P < 0.05$). Compared with control values, cortisol values increased more slowly, reaching significance at 30 min. There were no differences between groups. The AVP levels increased in all groups after 1 min and remained significantly elevated at all time periods measured. No significant differences were observed between treatment groups.

10 min after administration of fentanyl compared with both saline and esmolol.

Cortisol levels showed a gradual increase from 12.8 ± 3.7 μ g/dL at baseline to 25.6 ± 1.0 μ g/dL at 30 min after ECT, attaining significance for all groups ($P < 0.05$, Figure 3B). There were no significant differences between groups at any time period despite a trend toward lower cortisol levels after administration of fentanyl ($P < 0.06$, compared with saline or labetalol).

The largest neuroendocrine response to ECT measured in this study was the ECT-stimulated increase in AVP. The AVP levels increased significantly in all treatments at all time periods after induction of shock and seizure ($P < 0.0005$, Figure 3C). Mean plasma vasopressin levels increased from <2.0 pg/mL at

baseline to 55 ± 5.1 pg/mL at 1 min and then decreased to 3.0 ± 3 pg/mL (or barely detectable) at 30 min. The AVP response to ECT did not differ between groups. Surprisingly, there was no correlation between AVP levels and either BP or HR at any time during the study. The AVP levels also did not correlate significantly with ACTH or with the catecholamines measured at the same time or at subsequent post-ECT intervals.

Discussion

In part I of this study (2), the new β -adrenergic blockers labetalol and esmolol significantly attenuated the cardiovascular effects of ECT. In contrast, neither lidocaine nor fentanyl pretreatment had comparable ameliorating effects at the doses studied. In addition, esmolol did not significantly shorten seizure duration, whereas the other three pretreatment regimens did adversely affect the therapeutic benefit of ECT. Significant attenuation of the undesirable cardiovascular response to ECT could be due to pharmacologic blockade of the sympathetic outpouring commonly occurring after shock and seizure and/or to reduced peripheral and central response to circulating levels of catecholamines.

In this study, blood samples were collected at a limited number of time points for up to 30 min after seizure. One might argue that because of differences in kinetic properties of the five substances measured, samples should have been taken at different times for each substance and longer time points should have been measured. For example, the cortisol data are somewhat limited because of this hormone's rather slow and prolonged response to stressful interventions (14,15). However, because of the within-subjects study design, constraints on the total amount of blood that could be safely taken from individual patients, and the need to rapidly return the subjects back to the psychiatry ward, additional or later samples were simply not feasible. The five sampling time points were chosen to optimize the information obtained from all of the substances measured without compromising patient safety.

Electroconvulsive therapy induces a number of neuroendocrine responses in humans, including stimulation of prolactin, β -endorphin, ACTH, cortisol, and, possibly, growth hormone secretion (16). With respect to the pituitary-adrenal axis, preclinical studies suggest that repeated ECT treatments in laboratory animals increase the formation of corticotropin-releasing factor (CRF) mRNA in the hypothalamic paraventricular nucleus (17). This CRF-driven pituitary-adrenal activation during ECT, which resembles the neuroendocrine effects of chronic stress, may influence hypothalamic-pituitary-

adrenal (HPA) axis-sensitive processes mediating the therapeutic effect of ECT. Other hormones, such as thyroid-stimulating hormone and somatomedin A are not thought to be affected. Thus, ECT produces a selective response from the HPA axis.

The catecholamine response to ECT was first described by Gravenstein et al. (3). Since then, there have been several studies with similar results (4,5). Our results corroborate those reported earlier, with 3-fold and 15-fold increases observed for norepinephrine and epinephrine, respectively, immediately after seizure in patients receiving no premedication.

The HPA axis responds to a variety of "stressful" events by increasing CRF-mediated secretion of ACTH and cortisol. The duration of ECT-induced ACTH release (10-30 min) is longer than that seen for epinephrine and norepinephrine. The time-course for ACTH and cortisol responses to ECT also differ, with cortisol levels increasing slowly (30 min after ECT) in response to the earlier release of ACTH consistent with the cortisol responses to ACTH seen in other experimental paradigms.

The neuroendocrine response after ECT may be different from that after other procedures requiring anesthetics of similar duration. For example, Allen et al. (5) demonstrated a threefold increase in ACTH secretion after performance of ECT, but there was no such increase after cardioversion using a similar anesthetic technique. Thus, the increased ACTH secretion may be specific to ECT-induced activation of the central nervous system. Interestingly, despite the much shorter duration of the anesthetic, the magnitude of catecholamine and cortisol responses observed after ECT in the present study were similar to those previously measured during major upper abdominal (14,18) and coronary bypass operations (15).

Previous studies have demonstrated a relationship between AVP and systemic vascular resistance (SVR) (19), and, perhaps BP (20,21). No significant relationship between AVP and BP could be demonstrated in this study, possibly because of the premedications administered. Esmolol and labetalol both reduce the BP and HR responses to ECT. Significant differences in catecholamine levels were only seen, however, between esmolol and saline solution 1 min after seizure.

Fentanyl, which does not reliably blunt the cardiovascular response to ECT (2), significantly reduced norepinephrine levels at 1 min and ACTH levels at 1, 5, and 10 min. Opioids, including fentanyl, are thought to diminish the brain release of CRF (22), which could result in a reduction in ACTH secretion (15,23) during anesthesia. In addition, none of the pretreatments reliably blunted the increased cortisol seen at 30 min after ECT, although one might have expected this effect from at least fentanyl (24,25). This

may be due to the small sample size studied. Alternatively, it may be that none of the pretreatments blunted the eventual stress response. Similar results have been reported in studies comparing general with regional anesthetics (26).

In addition to CRF, AVP is an ACTH secretagogue that potentiates the effect of CRF (16). Consequently, ECT-stimulated release of AVP may be an important modulator of the ACTH response to ECT. Peripheral release of catecholamines during ECT may also stimulate the anterior pituitary glands to release ACTH (27), and this effect can be blocked by propranolol (28). Thus, β -adrenergic antagonists may have two effects on ACTH release during ECT: reduce the production of norepinephrine and epinephrine and antagonize the catecholamine's effect on ACTH-secreting cells in the anterior pituitary gland.

The relationship between catecholamine levels and hemodynamics during ECT appears to be more complex than that seen in some types of surgical anesthesia. Patients suffering from depression have diminished pituitary-adrenal responses to acute stresses and to CRF. The therapeutic effect of ECT has been correlated with normalization of the responsiveness of the pituitary-adrenal and sympathomedullary axes (17,29,30). This might be expected to result in larger cardiovascular responses to subsequent ECT treatments but, in fact, this does *not* occur (2). Furthermore, fentanyl does not reliably blunt the cardiovascular response to ECT but nevertheless reduces the catecholamine response. In contrast, fentanyl blunts both the hemodynamic and the catecholamine response to major surgery (31).

The lack of correlation observed between circulating levels of epinephrine or norepinephrine and HR could be due to the small sample studied, or may represent a more complex interaction of the two β -adrenergic antagonists esmolol and labetalol with the catecholamines. The administration of esmolol decreased release of norepinephrine, which seems to be most strongly correlated with the cardiovascular response to ECT. In addition, however, both esmolol and labetalol affect the peripheral response to catecholamines. Fentanyl, on the other hand, which appeared to block catecholamine release would not be expected to greatly alter their peripheral effect. Thus, esmolol and labetalol appear to be more effective in blunting the cardiovascular response to ECT primarily because of their peripheral effects. However, labetalol and esmolol may be somewhat different in this regard. For instance, labetalol, which did not decrease the release of norepinephrine in the patients sampled, nonetheless was nearly as effective as esmolol at blunting the cardiovascular response to ECT (2).

At least three confounding variables are involved

in the relationship between serum catecholamines and the cardiovascular response to ECT: the depressive state of the patient thought to affect both the release and the response to catecholamines (32); the administration of other cardiovascular drugs (such as esmolol), which may blunt both the release of catecholamines and their peripheral effects (33); and the effect of the general anesthetic.

This latter effect may explain why BP and, perhaps, HR increase during emergence from anesthesia, despite apparently decreasing levels of norepinephrine and epinephrine. Evidence for this comes from transthoracic impedance (Bomed) cardiac output measurements during ECT. The initial increase in BP and HR during ECT was accompanied by a decrease in cardiac output and an increase in SVR. In contrast, the increased BP seen during emergence was associated with increased cardiac output but little change in SVR (unpublished data). It may be that the initial BP increase is due to release of norepinephrine resulting in increased SVR, whereas the subsequent increase is the result of the diminishing cardiovascular depressant effects of the anesthetic as it redistributes in body tissue. Tachycardia, on the other hand, may be due to increases in serum epinephrine and/or reflex increases secondary to the drop in cardiac output.

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Depth of Placement of Left Double-Lumen Endobronchial Tubes

Jay B. Brodsky, MD, Jonathan L. Benumof, MD, Jan Ehrenwerth, MD, and George T. Ozaki

Departments of Anesthesiology, Stanford University School of Medicine, Stanford, California; University of California, San Diego, California; and Yale University School of Medicine, New Haven, Connecticut

Data on the normal depth of insertion of double-lumen tubes have not been published. We studied 101 adult patients undergoing thoracic operations whose tracheas were intubated with a left double-lumen tube. A fiberoptic bronchoscope was introduced into the tracheal lumen, and tube position was adjusted until the cephalad surface of the bronchial cuff was immediately below the carinal bifurcation. The average depth of insertion for both male and female patients 170 cm tall was 29 cm,

and for each 10-cm increase or decrease in height, average placement depth was increased or decreased 1 cm. The correlation between depth of insertion and height was highly significant ($P < 0.0001$) for both male and female patients. As depth of DLT insertion at any given height was normally distributed, a technique to confirm correct double-lumen tube position always should be used after initial placement.

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A poorly positioned double-lumen tube (DLT) can compromise any thoracic operation by preventing appropriate ventilation of the nonoperated lung or the selective collapse of the operated lung; the former can result in potentially life-threatening hypoxemia. The commonly used end points for depth of initial tube insertion, including a moderate increase in resistance to further passage down the bronchus and when the common molding that binds the two lumens together is at the incisors, are often inaccurate (1,2). Data on the normal range of depth for DLT insertion have not been published. Therefore we measured the depth of DLT placement in adult patients.

Methods

With the approval of the human subject committees at our institutions, 101 adult patients undergoing thoracic operations requiring tracheal intubation with a DLT consented to be studied.

Each patient was weighed and measured during the preoperative physical examination, and the information was recorded. In the operating room all

patients had their tracheas intubated with either a 35, 37, 39, or 41F left Broncho-Cath (Mallinckrodt, Argyle, N.Y.) DLT. After the tube was positioned in the left main bronchus, the bronchial cuff was inflated with air. A fiberoptic bronchoscope was then introduced into the tracheal lumen and advanced until either the tracheal carina or the endobronchial cuff was clearly visible. If necessary, the tube was withdrawn or advanced until the cephalad surface of the bright blue bronchial cuff was immediately below the carina. Insertion depth was measured using the external centimeter markings on the tube's lumen. Measurements were made at the corner of the mouth while the patient was in the supine position.

Statistical analysis for depth of DLT insertion was performed on a Macintosh computer using StatView II (Abacus Concepts, Calabasas, Calif.). A simple regression was calculated and the 95% confidence bands were plotted for the true mean of y . A P value of <0.05 was considered significant. The distribution of depth of DLT insertion for grouped intervals of height (short [136-164 cm], medium [165-179 cm], and tall [180-194 cm]) was also determined.

Results

There were 59 male and 42 female patients in the study. The results from all three institutions were almost identical and are pooled for presentation.

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Address correspondence to Dr. Brodsky, Department of Anesthesia, Stanford University Medical Center, Stanford, CA 94305.

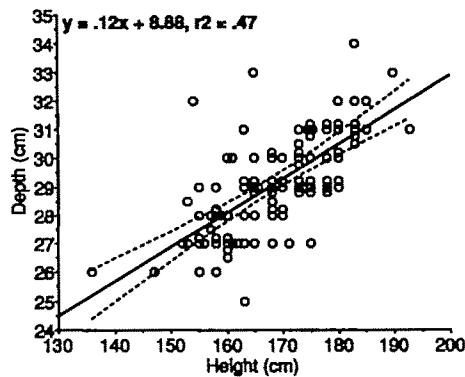


Figure 1. The regression line for depth of insertion (cm) of left double-lumen tubes versus height (cm) for all patients (male and female).

There was no correlation between depth of left DLT insertion with either age or weight for either men or women. However, there was a significant correlation of depth of insertion with height for both male and female patients. The regression lines and P values for men and women separately were nearly identical and were $y = 0.11x + 10.53$, $R^2 = 0.28$, $P < 0.01$, and $y =$

$0.11x + 10.94$, $R^2 = 0.31$, $P < 0.001$, respectively. Figure 1 shows the depth of insertion versus height regression line data for all patients (male and female); the correlation was highly significant ($P < 0.0001$). The average depth of insertion was 29 cm for patients 170 cm tall. For every 10-cm increase or decrease in height, the average depth for DLT placement was increased or decreased 1 cm. Figure 2 shows the distribution of depth of insertion for all patients and for three grouped intervals of patient height. At each grouped interval of patient height, the distribution of depth of insertion was normally distributed. Figure 3 demonstrates that as patient height increased, the size of the DLT chosen increased.

Discussion

Two of the most common problems associated with DLT placement are insertion either insufficiently far or too deeply into the appropriate bronchus (3). This study attempts to define a range of depth for left-DLT insertion to reduce these problems. A left DLT was used for both right and left thoracotomies because the "margin of safety" is greater if the longer left main

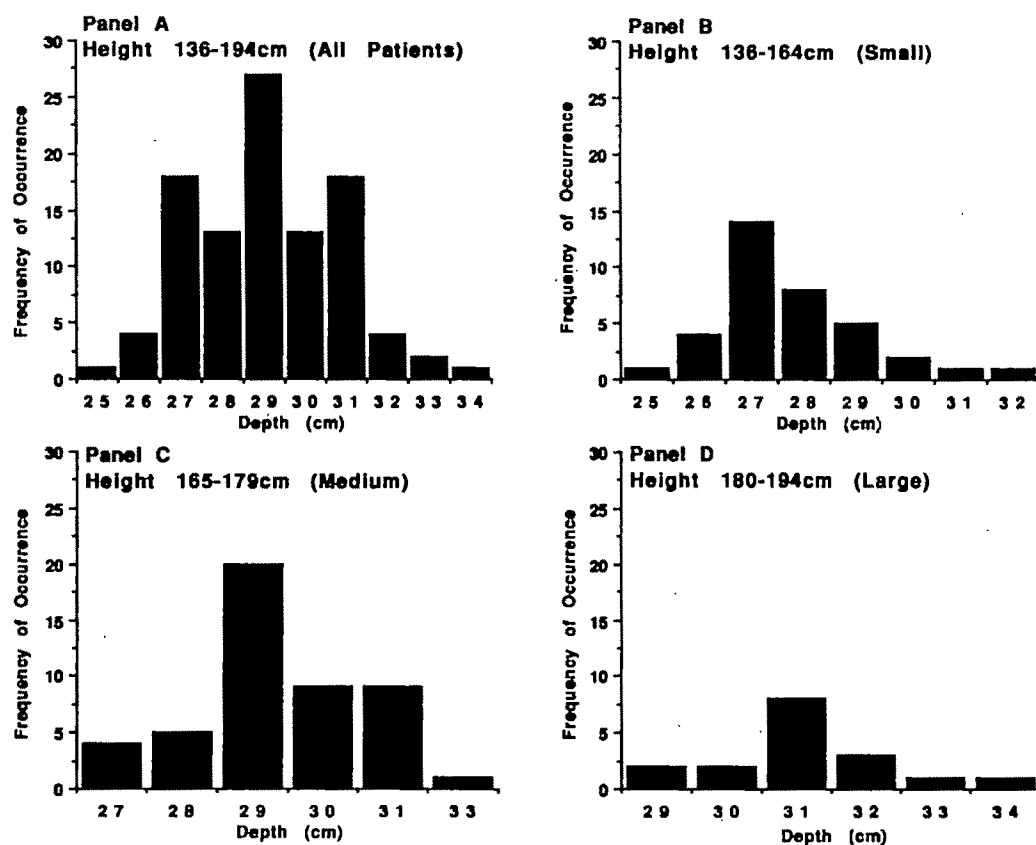


Figure 2. The depth of insertion (cm) for left double-lumen tubes for all patients and for three grouped intervals based on patient height (cm). At each grouped interval the distribution of depth of insertion was normally distributed.

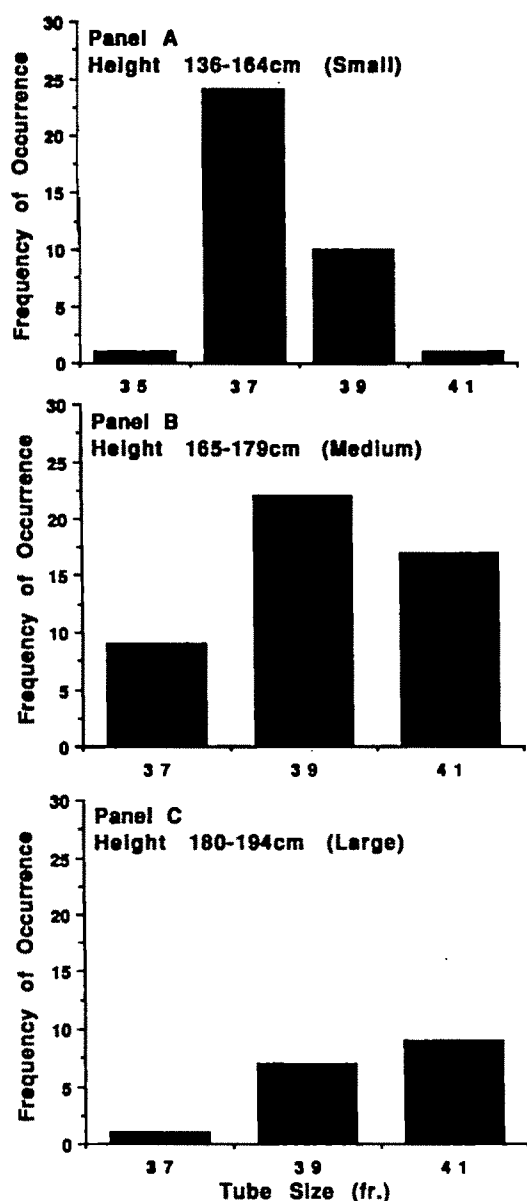


Figure 3. Larger double-lumen tubes were chosen as patient height increased.

bronchus is intubated (4). Right DLTs must be considered separately.

Optimal DLT depth was defined as when the blue endobronchial cuff was just below the carina, because if the cuff were more proximal it would obstruct the trachea and the contralateral right-main bronchus (5). If the cuff were deeper, the left-upper lobe bronchus could be obstructed (6).

We found that as patient height increases, the optimal depth of DLT insertion increases. However, as the depth of insertion at any given height was normally distributed, our data are useful only as a guide and should not be used as the end point for final tube placement. Once the tube is placed, it is mandatory that a technique for confirmation of position be used. Reassessment and readjustment after placing the patient in the lateral decubitus position is also essential. Finally, it is important to recognize that these tubes can move distally with head flexion or proximally with head extension and can be displaced even further by manipulation during surgery (7).

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Pulmonary Artery Catheter Introducers: Do the Component Parts Affect Flow Rate?

Steve A. Hyman, MD, David W. Smith, MD, Roger England, BS, Rebecca Naukam, BS, and M. Lawrence Berman, MD, PhD

Department of Anesthesiology, Vanderbilt University, Nashville, Tennessee

Arrow sheath introducers are useful during massive transfusion as well as during catheter insertion. However, each component (sheath, side port, and obturator/catheter) probably progressively impedes maximum flow. This study quantitates these flow changes. Six configurations (C) were tested: (C1) sheath; (C2) sheath, side port; (C3) sheath, side port, obturator; (C4) C3 with 1.5-in obturator; (C5) C3 with 0.25-in obturator; (C6) no components. Flow was measured five times with each configuration and compared. Flows (mL/min) (mean \pm SE) were: (C1) 838.1 ± 11.2 , (C2) 283.4 ± 9.2 , (C3) 149.9 ± 7.9 , (C4)

176.0 ± 14.0 , (C5) 232.5 ± 5.5 , (C6) 1030.5 ± 11.6 . Flow decreased progressively with C2 and C3 ($P < 0.0001$). C4 did not increase flow, but C5 did ($P < 0.0001$). C5 flow was comparable to C2 but less than C1 ($P < 0.0001$). C6 flow was larger than any other configuration ($P < 0.0001$). Flow increases in C2 and C5 over C3 and C4 were modest (25%–50%) compared with C1 (250%). Therefore, we do not recommend removing or cutting the obturator to improve flow. During massive transfusion, we recommend removal of the side port until smaller flows suffice.

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As a level 1 trauma center, our hospital accepts referrals of multiply traumatized patients who frequently require intravascular administration of blood and crystalloids in large quantities. Despite the severity of some injuries, lives are saved by appropriate replacement of oxygen carrying capacity and intravascular volume. Large-bore intravenous catheters (e.g., 12 or 14 gauge) are often inadequate during massive transfusion (1) for hemorrhage of this magnitude. Pulmonary artery catheter introducers, by virtue of their large diameter, are well suited for rapid administration of large fluid volumes.

Arrow percutaneous sheath introducer kits (Arrow International, Reading, Pa.) have an 8.5F lumen with introducer sheath. A separate side port assembly has a self-sealing hemostasis valve for insertion of a pulmonary artery or central venous pressure catheter. Conahan et al. (2) suggest that the self-sealing valves in this system appear to remain competent

when exposed to vacuums of -30 cm H_2O . Thus, the valve should not leak when exposed to negative intrathoracic pressure. However, there is no assurance that this valve, even when new, is competent to prevent air emboli (3–5). Because of this inherent risk, an obturator with an airtight cap should be inserted through the valve when a central catheter is not in place. The obturator, unfortunately, appears to reduce the maximum infusion rate, so some clinicians shorten it, presumably to restore a more rapid flow. The actual flow reduction caused by the obturator is unclear.

A complete introducer device has three components: the sheath, the side port/hemostasis valve, and the obturator (Figure 1). The goals of this study were threefold. First, to determine the flow changes caused by the side port/hemostasis valve; second, to determine if the obturator further reduced flow; and third, to determine if the latter changes were reversible by shortening the obturator.

Methods

The percutaneous sheath introducer assembly was attached to an intravenous administration set using six different component configurations (C):

C1. Sheath only, no side port

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Introducers were provided by Arrow International, Reading, Pennsylvania.

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Address correspondence to Dr. Hyman, Department of Anesthesiology, Vanderbilt University, Nashville, TN 37232-2125.

- C2. Sheath and side port, no obturator
C3. Sheath and side port, uncut obturator inserted through hemostasis valve
C4. Same as C3, but obturator cut to a length of 1.5 in
C5. Same as C3, but obturator cut to a length of 0.25 in
C6. No components

Flow was measured five times with each configuration. A new introducer kit was used for each flow determination.

An intravenous fluid administration bag containing approximately 1 L of tap water was hung 36 in above the assembly. Extending from the bag was a large-bore vinyl tubing with a non-Luer lock-type connector at the end. The time (T) for the fluid to drain into a beaker was measured with a stopwatch. The drained water was weighed (V). The specific gravity of water is 1, so 1 g equals 1 mL. Flow was calculated using Equation (1):

$$\text{Flow (mL/min)} = \frac{V}{T} \times 60.$$

Certain infusion systems, particularly those using 3-mm tubing, reduce maximum flow rate (6,7). To prove that the present setup did not influence maximum flow, we measured flow with no components attached (C6).

Flow rates determined with each system configuration were compared using analysis of variance. Differences were considered significant if $P < 0.05$. Tukey's honestly significant differences test was the multiple range test when significant differences were

Table 1. Flow Through Sheath/Side Port/Hemostasis Valve Assembly

Configuration	No. of trials	Mean flow (mL/min)	SEM
C1	5	838.1 ^a	11.2
C2	5	238.4 ^b	9.2
C3	5	149.9 ^c	7.9
C4	5	176.0 ^c	14.0
C5	5	232.5 ^b	5.5
C6	5	1030.5 ^a	11.6

SEM, standard error of the mean; C1, sheath only, no side port; C2, sheath and side port, no obturator; C3, sheath and side port, uncut obturator inserted through hemostasis valve; C4, same as C3, but obturator cut to a length of 1.5 in; C5, same as C3, but obturator cut to a length of 0.25 in; C6, no sheath or side port/hemostasis valve.

^aSignificantly different from all other configurations.

^bSignificantly different from configurations 1, 3, 4, and 6 ($P < 0.0001$).

^cSignificantly different from configurations 1, 2, 5, and 6 ($P < 0.0001$).

found. Statistics were performed using Statgraphics (STSC, Inc., Rockville, Md.).

Results

The flow through the system with C6 was 1030 ± 11.6 mL/min (mean \pm SE) (Table 1). This flow was significantly larger ($P < 0.0001$) than C1 (838 ± 11 mL/min). It is, therefore, unlikely that the intravenous bag or tubing influenced maximum flow. With C2, flow decreased significantly to 238 ± 9 mL/min ($P < 0.0001$). Flow decreased even further with C3 (150 ± 8 mL/min). Cutting the obturator at a length of 1.5 in (C4) did not increase flow rate, but cutting it to a length of less than 0.25 in (C5) resulted in a significant increase in flow ($P < 0.0001$).

Discussion

A percutaneous introducer sheath with a side port/hemostasis valve assembly affords the ability to easily insert a pulmonary artery or central venous pressure catheter plus maintain an intravenous infusion port. When the catheter is not in place, an airtight obturator should be inserted instead. The obturator, in addition to sealing the hemostasis valve, prevents kinking of the sheath. Such kinking may occur at the skin insertion site or where the sheath passes by the clavicle when using a subclavian route.

Flow through the side sheath/port/hemostasis valve system is significantly reduced by the presence of the uncut obturator. Flow is not increased by shortening the obturator length to 1.5 in but is increased when the obturator length is shorter than 0.25 in. The reason for this is demonstrated in Figure 2. When the length is longer, the obturator passes through the area where the side port drains into the

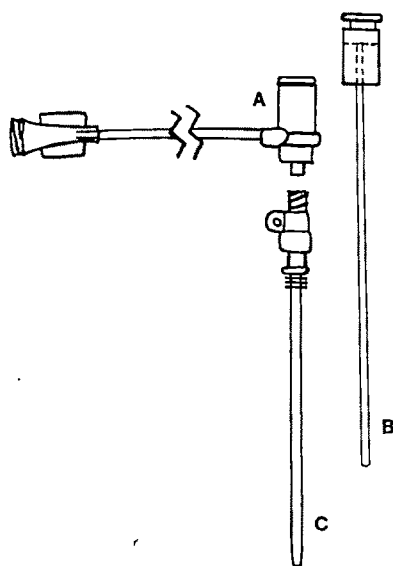


Figure 1. A complete introducer device has three components: the side port/hemostasis valve (A), the obturator (B), and the sheath (C).

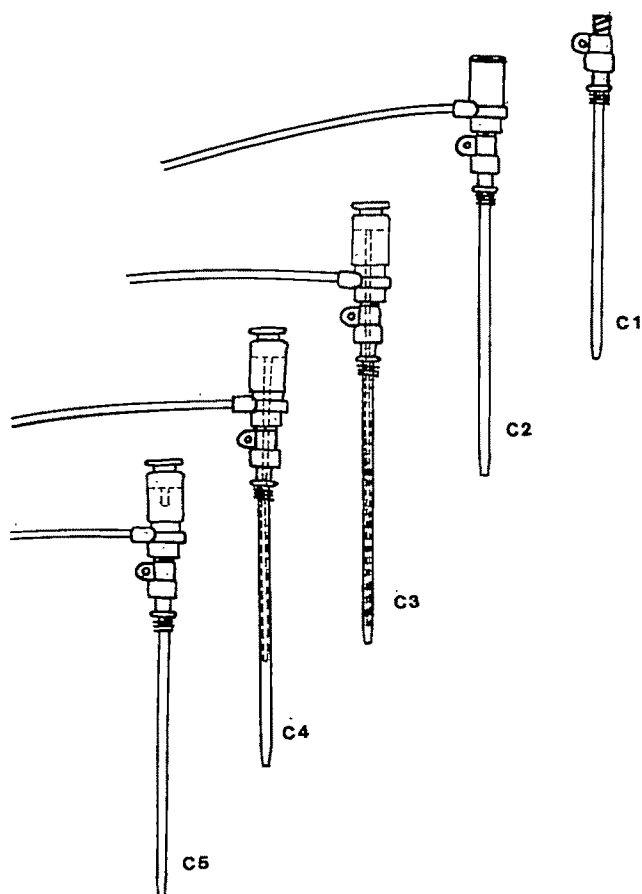


Figure 2. Six configurations (C) of pulmonary artery catheter introducer components were assembled to test flow from an intravenous fluid administration assembly. (C1) sheath; (C2) sheath, side port; (C3) sheath, side port, obturator; (C4) C3 with 1.5-in. obturator; (C5) C3 with 0.25-in. obturator. A sixth configuration (C6) with no components attached was also tested.

sheath. Flow decreases, presumably by obstruction of the side port orifice or by increased turbulence in the sheath. When the obturator is very short, it fails to reach the orifice, and flow rate is similar to that without an obturator. Despite its statistical significance ($P < 0.0001$), the flow increase after shortening or removing the obturator is modest. Flow increased by approximately 25%–50% (56–92 mL/min), but this increase was small in comparison with that found when the side port/hemostasis valve was removed altogether. Changing from C2 to C1 results in an

increase of approximately 600 mL/min (250%). Clearly an increase of this magnitude is more likely to improve outcome in exsanguinating injuries.

We do not recommend shortening the obturator and believe that this is a potentially dangerous practice. Small fragments of plastic material could remain attached to the obturator after removal of the tip. These fragments could enter the pulmonary vasculature, or worse, the arterial system if there were a right-to-left shunt. A shortened obturator can also cause confusion during removal. The clinician inserting the sheath and obturator is often not the one who removes it. If the latter is unaware that the obturator is shortened, he or she may incorrectly assume that it was inadvertently broken off inside the patient. This could result in unnecessary radiologic or surgical exposure for a nonexistent problem. Finally, in the event that a patient were injured by the introducer assembly, it is unlikely that the manufacturer would stand behind the product in its altered state.

In conclusion, flow through a pulmonary artery catheter introducer sheath is decreased by approximately 600 mL/min by attaching a side port/hemostasis valve assembly. Flow is further reduced by inserting an intact obturator or one cut to 1.5 in, but not by one cut to less than 0.25 in. We do not recommend removing the obturator or shortening it to improve maximum flow rates. However, if very large flow rates are necessary, we recommend completely removing the side port/hemostasis valve until smaller flow rates are adequate.

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Arterial and Mixed Venous Blood Acid-Base Balance During Hypoperfusion With Incremental Positive End-Expiratory Pressure in the Pig

A. B. Johan Groeneveld, MD, PhD, Cornelis G. Vermeij, MD, and Lambertus G. Thijs, MD, PhD

Medical Intensive Care Unit, Free University Hospital, Amsterdam, The Netherlands

The authors sought to determine how hypoperfusion influences acid-base balance in arterial and mixed venous blood. In anesthetized, ventilated pigs ($n = 12$), we determined hemodynamics, O_2 uptake, CO_2 output, dead-space ventilation, arterial and mixed venous blood acid-base balances, and lactate concentrations during graded reductions in cardiac output by incremental positive end-expiratory pressure (PEEP, 0–20 cm H_2O). Cardiac output decreased from 3.2 ± 0.2 (mean \pm SEM) to 1.2 ± 0.1 L/min at 20 cm H_2O PEEP. Oxygen delivery declined more than O_2 uptake did by $60\% \pm 2\%$ and $27\% \pm 2\%$, respectively. The decrease in CO_2 output (by $21\% \pm 2\%$) was less than that in O_2 uptake. Fractional dead-space ventilation increased. At a slight increase in carbon dioxide tension (P_{CO_2}) of 4 ± 1 mm Hg, pH decreased in arterial blood from 7.54 ± 0.01 to 7.47 ± 0.02 mmol/L, and standard bicarbonate decreased from 30.3 ± 0.5 to 27.5 ± 0.6 mmol/L. The decrease in standard bicarbonate exceeded the increase in blood lactate

concentrations. At a similar decrease in standard bicarbonate, the decrease in pH was larger ($P < 0.005$) in mixed venous blood than in arterial blood owing to a larger increase in P_{CO_2} (from 40 ± 2 to 50 ± 2 mm Hg, $P < 0.005$). The changes were reversed after discontinuing PEEP. The authors conclude that ischemia after incremental PEEP results in tissue metabolic acidosis with superimposed respiratory acidosis. This is not caused by increased tissue production or by impaired pulmonary excretion of CO_2 but by a larger decrease in blood flow than in CO_2 production in the tissues, so that CO_2 stores increase. Decreased pulmonary blood flow and increased dead-space ventilation prevent a decrease in arterial P_{CO_2} by diminished CO_2 production. A smaller reduction in CO_2 production than in O_2 uptake is only partly explained by bicarbonate buffering of lactic acid.

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In the presence of adequate ventilation, changes in blood acid-base balance during cardiac arrest and resuscitation have been attributed mainly to metabolic deterioration with resultant lactic acidosis (1–5). Recently, however, several authors have suggested that, at least shortly after cardiac arrest and resuscitation, respiratory instead of metabolic acidosis may prevail in the tissues as pH may be low after a high carbon dioxide tension (P_{CO_2}) in mixed venous blood, whereas respiratory alkalosis after a decrease in P_{CO_2} may predominate in arterial blood (6–12). The mixed venous P_{CO_2} indeed reflects the mean tissue P_{CO_2} because CO_2 is freely diffusible across cell membranes (6,7,11,12). A widening of arteriovenous P_{CO_2}

and pH gradients occurs also during other low-flow states (8,10,13–18).

In many studies, intravenous administration of CO_2 -generating sodium bicarbonate (4,6,8) or development of hyperventilation (6–12,17), leading to an increase in P_{CO_2} in mixed venous blood or a decrease in P_{CO_2} in arterial blood, respectively, may have contributed to widening of the arteriovenous P_{CO_2} (and pH) gradient during hypoperfusion (8,10,17). This may have confounded the assessment of acid-base changes after a reduction in cardiac output alone and may have obscured metabolic, superimposed on respiratory, acid-base changes (5). In some studies, a decrease in blood flow at constant arterial P_{CO_2} resulted in predominating metabolic acidosis in venous blood or tissue despite a high P_{CO_2} in the latter (11,13–16,19). This respiratory, superimposed on metabolic, acidosis could be caused by an elevated CO_2 production through bicarbonate buffering of

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Address correspondence to Dr. Groeneveld, Medical Intensive Care Unit, Free University Hospital, De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands.

lactic acid (11,13-16,19) or by impaired pulmonary excretion of CO_2 (6,7,9-11,17,18,20-22). Finally, many studies do not allow conclusions on hypoperfusion-induced changes in acid-base equilibrium under steady-state conditions (6-12).

As the effects of hypoperfusion on acid-base balance and their mechanisms are unclear, we measured arterial and mixed venous acid-base balance, blood lactate concentrations, O_2 delivery and uptake, CO_2 production, and dead-space ventilation in a porcine model of graded hypoperfusion (at constant ventilatory minute volume) induced by incremental positive end-expiratory pressure (PEEP).

Methods

Twelve male Yorkshire pigs, weighing 23 ± 1 kg, were studied. Before the experiments, the animals fasted for 24 h but were allowed free access to water. Anesthesia was induced with the butyropheneone azaperone (2 mg/kg intramuscularly) and with thiopental (20 mg/kg intravenously) and maintained with a continuous infusion of pentobarbital ($5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and pancuronium bromide ($0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) for muscular paralysis (23). After tracheal intubation, ventilation was controlled: tidal volume was 15 mL/kg at a frequency of 12 breaths/min (inspired oxygen fraction, 40%; Servo 900 B ventilator, Siemens, Stockholm, Sweden). Frequency was adjusted to obtain a normal pH of about 7.50 in arterial pig blood (24). After initial adjustments, these ventilatory settings were not changed during the experiments. The Animal Investigation Committee of the Free University approved the protocol.

Pigs were studied in the supine position on a heating blanket. Continuous recording of the electrocardiogram allowed the calculation of heart rate (HR). A catheter was placed in the right carotid artery for measurement of mean arterial pressure (MAP). A 7F flow-directed pulmonary artery catheter was advanced into the pulmonary artery through the right external jugular vein for the measurement of body temperature and cardiac output (CO) using the thermodilution technique and a computer (REF 1, Edwards Laboratories, Santa Ana, Calif.). The mean of three determinations at end-expiration, using injections of 5 mL of iced 5% dextrose, was used. Arterial and mixed venous blood samples were drawn simultaneously in heparinized syringes, placed on ice, and sent immediately to the laboratory for determination of pH, O_2 and CO_2 tensions, and standard bicarbonate ($\text{st}[\text{HCO}_3^-]$, at 40 mm Hg Pco_2) taking body temperature into account (Corning type 175, American Hospital Supply). Respiratory acid-base changes were defined on the basis of changes in Pco_2 and metabolic acid-base changes, on the basis of alterations in $\text{st}[\text{HCO}_3^-]$, regardless of their cause and

the origin of the blood (arterial versus mixed venous) in which measurements were done. Hemoglobin (Hb) and O_2 saturation (So_2) were also measured (Co-oximeter, Instrumentation Laboratories, Lexington, Mass.). Oxygen content in arterial blood (Cao_2) was calculated from $1.39 \times \text{Hb} \times \text{So}_2 + 0.0031 \times \text{Po}_2$. Oxygen delivery ($\dot{\text{V}}\text{O}_2$) was defined as the product of CO and Cao_2 . Arterial blood lactate concentrations were measured with an enzymatic method (Analytical Chemistry Analyzer, Dupont, Wilmington, Del.).

Expiratory minute volume (V_E), O_2 uptake ($\dot{\text{V}}\text{O}_2$), and CO_2 output, assumed to reflect CO_2 production ($\dot{\text{V}}\text{CO}_2$) at standard temperature, pressure, and dry gas conditions were measured each minute with a Deltatrac metabolic monitor (Datex, Helsinki, Finland) (25). The monitor was connected to the outlet of the ventilator, and expired gas was collected in a mixing chamber. The monitor samples inspired air, and a paramagnetic differential O_2 sensor measures the inspired O_2 concentration (Fio_2) and the difference between inspired and expired O_2 concentration ($\text{Fio}_2 - \text{FeO}_2$). The mixed expired CO_2 concentration is measured continuously with an infrared sensor. Before measurements were taken, the sensors were calibrated with a gas mixture of known composition. The metabolic monitor showed inaccuracy of the $\dot{\text{V}}\text{O}_2$ and $\dot{\text{V}}\text{CO}_2$ measurements of less than 2% at Fio_2 of 40% and PEEP of up to 20 cm H_2O , using previously described methods (26). The FECO_2 was converted to the mixed expiratory Peco_2 for computation of fractional dead-space ventilation ($\text{V}_\text{d}/\text{V}_\text{t}$) from (arterial $\text{Pco}_2 - \text{Peco}_2$)/arterial Pco_2 .

Measurements were performed at $t = 0$ min and were repeated at $t = 30$ min, after which PEEP was increased by 5-cm H_2O increments at 15-min intervals from 0 to 20 cm H_2O ($t = 90$ min), to lower CO and $\dot{\text{V}}\text{O}_2$ (27), each time preceded by measurements using final 5-min averages for V_E , $\text{V}_\text{d}/\text{V}_\text{t}$, $\dot{\text{V}}\text{O}_2$, and $\dot{\text{V}}\text{CO}_2$. At $t = 90$ min, PEEP was discontinued, followed by measurements at $t = 120$ and 150 min, after which the animals were killed by injection of saturated potassium chloride solution.

Values are presented as mean \pm SEM. Changes in variables compared with $t = 30$ min were assessed with analysis of variance for repeated measurements. If statistical significance was reached, the Wilcoxon signed-rank test for paired data was used. Linear regression analysis was used for computing correlation coefficients. A $P < 0.05$ was considered statistically significant.

Results

Graded increases in PEEP decreased CO (by 2.0 ± 0.2 L/min or $62\% \pm 2\%$ at 20 cm H_2O PEEP) and MAP

Table 1. Hemodynamic, Metabolic, and Ventilatory Variables During Incremental Positive End-Expiratory Pressure in 12 Pigs

Variables	PEEP (cm H ₂ O)							
	0	0	5	10	15	20	0	0
Time (min)	0	30	45	60	75	90	120	150
Heart rate (beats/min)	87 ± 4	94 ± 4	110 ± 5 ^a	115 ± 5 ^a	126 ± 7 ^a	133 ± 8 ^a	92 ± 6	98 ± 7
Mean arterial pressure (mm Hg)	103 ± 5	103 ± 4	93 ± 5 ^b	81 ± 6 ^a	68 ± 6 ^a	53 ± 3 ^a	118 ± 4 ^b	114 ± 5 ^c
Cardiac output (L/min)	3.26 ± 0.26	3.19 ± 0.24	3.02 ± 0.25	2.29 ± 0.23 ^a	1.60 ± 0.14 ^a	1.21 ± 0.11 ^a	3.11 ± 0.35	3.12 ± 0.34
Oxygen delivery (mL/min)	391 ± 21	394 ± 22	379 ± 28	288 ± 26 ^a	203 ± 15 ^a	157 ± 11 ^a	389 ± 35	382 ± 32
Oxygen uptake (mL/min)	159 ± 13	155 ± 11	152 ± 11 ^b	138 ± 8 ^a	125 ± 8 ^a	113 ± 8 ^a	163 ± 13	160 ± 12
Carbon dioxide output (mL/min)	119 ± 10	113 ± 9	112 ± 9	103 ± 7 ^a	97 ± 7 ^a	89 ± 6 ^a	129 ± 10 ^a	120 ± 9 ^a
Lactate (mmol/L)	1.9 ± 0.2	1.5 ± 0.1	1.5 ± 0.2	1.6 ± 0.2	1.9 ± 0.2 ^b	2.5 ± 0.3 ^a	2.4 ± 0.3 ^a	1.8 ± 0.2
Temperature (°C)	36.8 ± 0.35	36.9 ± 0.36	37.0 ± 0.37 ^c	37.1 ± 0.40 ^c	37.1 ± 0.38 ^c	37.0 ± 0.38	37.3 ± 0.40 ^b	37.5 ± 0.40 ^a
Ventilatory minute volume (L/min)	4.4 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.1 ^c	4.5 ± 0.1 ^c	4.4 ± 0.1
Dead-space ventilation/tidal volume	0.32 ± 0.02	0.33 ± 0.02	0.36 ± 0.02	0.39 ± 0.02 ^b	0.42 ± 0.02 ^b	0.52 ± 0.01 ^a	0.32 ± 0.02	0.34 ± 0.02

PEEP, positive end-expiratory pressure.

Values are mean ± SEM.

^a*P* < 0.005 versus *t* = 30 min.^b*P* < 0.01 versus *t* = 30 min.^c*P* < 0.05 versus *t* = 30 min.

and increased HR (Table 1). Because arterial P_{O_2} and SO_2 were unchanged at 20 cm H₂O PEEP, the reduction in tissue $\dot{D}O_2$ by $60\% \pm 2\%$ paralleled the decrease in CO. Despite a decrease in mixed venous P_{O_2} and SO_2 , and thus increased tissue O_2 extraction ratio (to $73\% \pm 4\%$ at 20 cm H₂O PEEP), $\dot{V}O_2$ declined by $27\% \pm 2\%$ at 20 cm H₂O PEEP. Body temperature slightly increased during the experiments. Although the arterial lactate concentration at *t* = 0 min was slightly elevated, possibly as a consequence of anesthesia and instrumentation, the concentration increased during incremental PEEP, as compared with *t* = 30 min before PEEP. Although \dot{V}_E slightly declined (by $3\% \pm 1\%$), $\dot{F}ECO_2$ decreased (from $2.58\% \pm 0.18\%$ at 0 cm H₂O to $2.01\% \pm 0.11\%$ at 20 cm H₂O PEEP, *P* < 0.005), so that $\dot{V}CO_2$ decreased by $21\% \pm 2\%$. The latter declined less than $\dot{V}O_2$, and the respiratory quotient (RQ) increased (from 0.72 ± 0.01 before PEEP to 0.77 ± 0.01 at 15 cm H₂O and to 0.79 ± 0.03 at 20 cm H₂O PEEP, *P* < 0.01). There was also an increase in \dot{V}_d/\dot{V}_t .

At 20 cm H₂O PEEP, both pH and $st.[HCO_3^-]$ declined in arterial blood (Figure 1). The pH decreased more in mixed venous blood than in arterial blood; the gradient increased from 0.045 ± 0.003 at 0 cm H₂O PEEP to 0.083 ± 0.008 at 20 cm H₂O PEEP. The decrease in $st.[HCO_3^-]$ in mixed venous blood was comparable to that in arterial blood. The arterial P_{CO_2} slightly increased by 4 ± 1 mm Hg at 20 cm H₂O PEEP. The increase in mixed venous P_{CO_2} , however, exceeded that in arterial blood; the gradient increased from 7 ± 1 at 0 cm H₂O PEEP to 14 ± 1 mm Hg at

20 cm H₂O PEEP. The mean arteriovenous P_{CO_2} gradient at the time points of our study were inversely related to the mean CO (Figure 2A).

Changes in most variables, including elevated arteriovenous gradients, reversed after PEEP was discontinued. At *t* = 120 min, there was an overshoot in MAP (by 15 ± 4 mm Hg) and in \dot{V}_E (by $3\% \pm 1\%$), transiently reaching values above baseline (*t* = 30 min). Arterial and mixed venous P_{CO_2} were higher and pH was lower during reperfusion after PEEP compared with *t* = 30 min before PEEP, whereas CO, \dot{V}_d/\dot{V}_t , arteriovenous P_{CO_2} and pH gradients, and $st.[HCO_3^-]$ had returned to baseline values. At *t* = 120 min after PEEP, there was an increase in $\dot{F}ECO_2$ (to $2.83\% \pm 0.17\%$) and in $\dot{V}CO_2$ (by $14\% \pm 2\%$) above baseline values at *t* = 30 min (*P* < 0.005). The increase in $\dot{V}CO_2$ was greater (*P* < 0.005) than that in $\dot{V}O_2$ (by $5\% \pm 2\%$, *P* = 0.06) and the RQ was still elevated (0.79 ± 0.01 , *P* < 0.005 versus *t* = 30 min).

The decrease in $\dot{V}CO_2$ during hypoperfusion did not significantly differ from the decrease in the product of the arteriovenous P_{CO_2} gradient and CO (by $30\% \pm 7\%$ at 20 versus 0 cm H₂O PEEP). Figure 2B shows that the mean $\dot{V}CO_2/CO$ ratio at the time points of the study directly related to the mean arteriovenous P_{CO_2} gradient, so that changes in the calculated arteriovenous CO_2 content difference (Fick principle) paralleled the P_{CO_2} gradient during our experiments.

The decline in $st.[HCO_3^-]$ during hypoperfusion exceeded the increase in lactate (by 1.9 ± 0.4 mmol/L at 20 cm H₂O PEEP, *P* < 0.005). The mean $st.[HCO_3^-]$ concentration (B) at the time points of the study in-

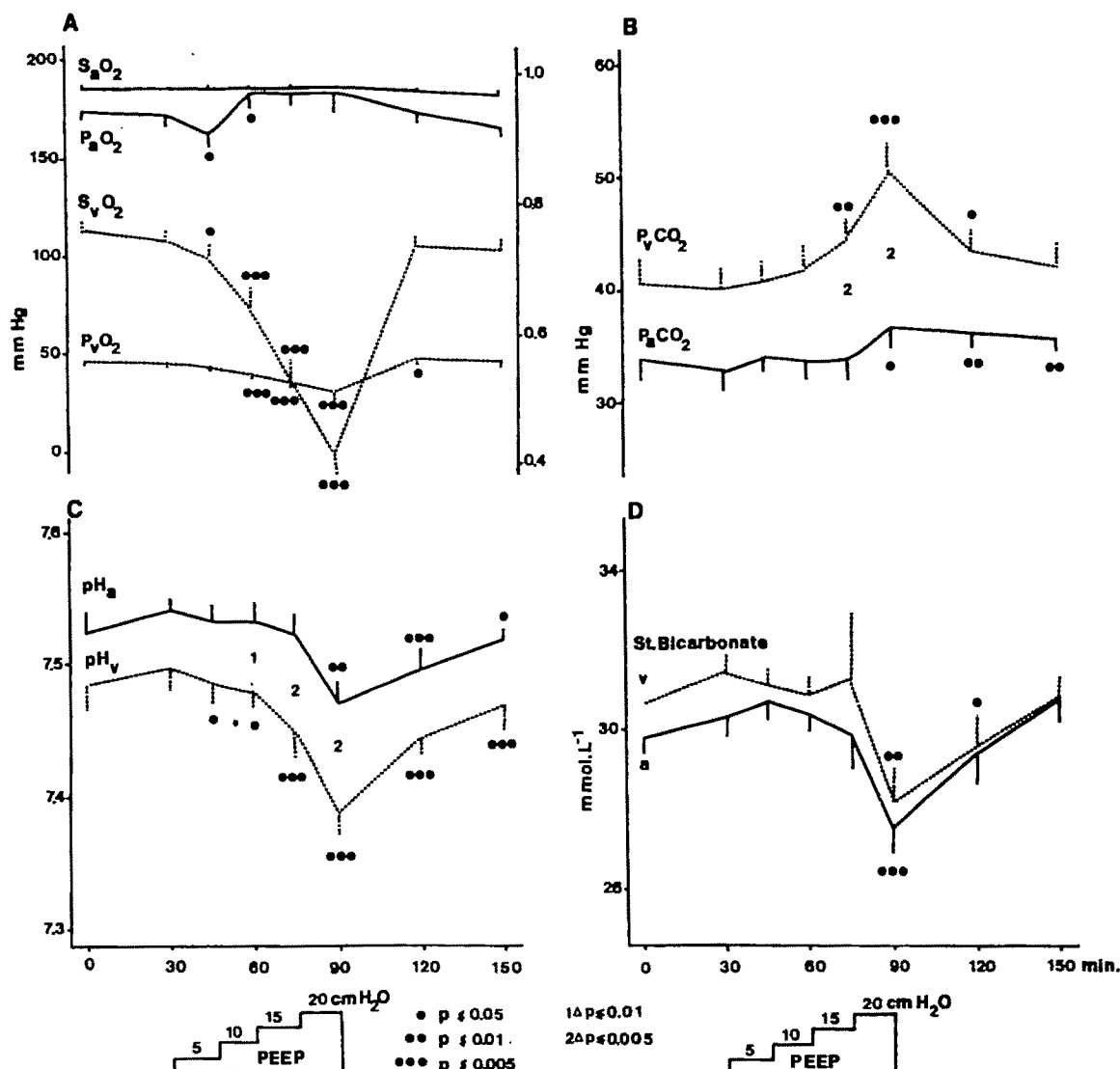


Figure 1. Mean \pm SEM (in 12 pigs) of values in arterial and mixed venous blood and their arteriovenous gradient (Δ) during incremental positive end-expiratory pressure (PEEP) for (A) partial O_2 tension (PO_2) and saturation (SO_2), (B) partial CO_2 tension (P_{CO_2}), (C) pH, (D) standard bicarbonate concentration.

versely correlated with the mean lactate (L) concentration: $B = 34.3 - 2.3L$, $r = -0.85$, $P < 0.01$, so that on a molar basis, changes in lactate accounted for only 44% of changes in $st.[HCO_3^-]$ during our experiments. The mean RQ also correlated with the mean lactate concentration, whether rising (net production) or decreasing (net uptake during reperfusion): $RQ = 0.69 + 0.034L$, $r = 0.74$, $P < 0.05$, so that about 50% ($=r^2$) of changes in RQ could be explained by changes in lactate.

Discussion

Graded reductions in CO with incremental PEEP thus decrease tissue $\dot{V}O_2$ despite increased O_2 extraction, and increase lactate concentrations. The decrease in

pH and $st.[HCO_3^-]$ and the increase in P_{CO_2} in mixed venous blood indicate development of metabolic acidosis with superimposed respiratory acidosis in the tissues. Arterial blood only shows the development of metabolic acidosis, as pH and $st.[HCO_3^-]$ decrease at almost constant P_{CO_2} . At equal decreases in $st.[HCO_3^-]$ in arterial and mixed venous blood, the elevated arteriovenous P_{CO_2} gradient accounts for the increased pH gradient.

The arteriovenous P_{CO_2} gradient was elevated despite a diminished $\dot{V}CO_2$ during hypoperfusion. Assessment of tissue CO_2 production from expired gas is only valid if CO_2 stores in the body are in steady-state (15,28,29). After each PEEP increment, $\dot{V}CO_2$ (and $\dot{V}O_2$) decreased almost instantaneously and

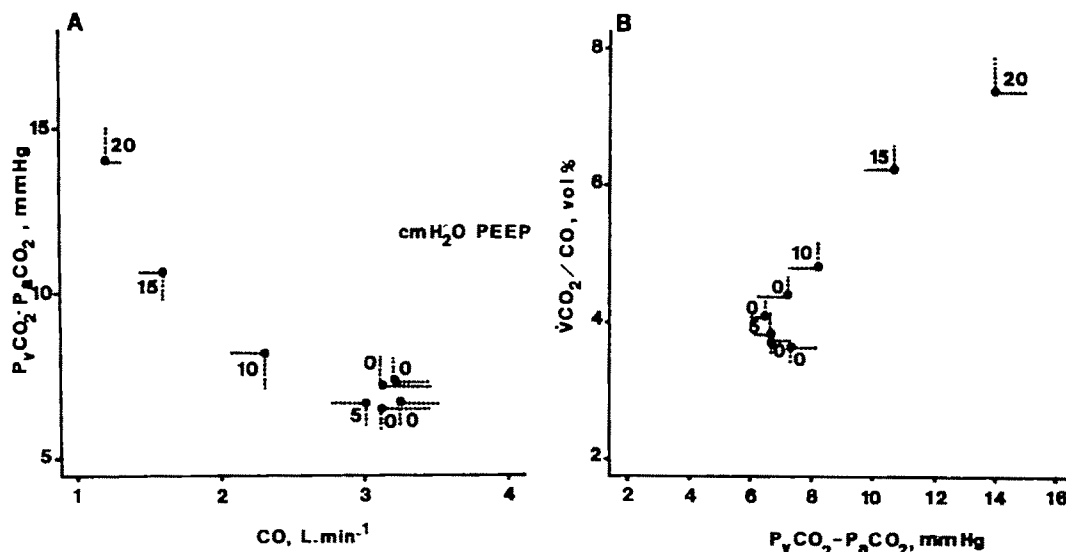


Figure 2. (A) Relation between the arteriovenous Pco₂ gradient and cardiac output (CO): Pco₂ - gradient = 16.5 - 3.12CO, $r = -0.95$, $P < 0.005$. Mean \pm SEM. (B) Relation between CO₂ output ($\dot{V}CO_2$) divided by cardiac output and the arteriovenous Pco₂ gradient: $\dot{V}CO_2/CO = 0.52 + 0.50(P_{v}CO_2 - P_{a}CO_2)$, $r = 0.97$, $P < 0.005$. Mean \pm SEM.

varied only 2% during the final 5 min of the 15-min PEEP intervals. During hypoperfusion, the decrease in $\dot{V}CO_2$ was comparable to the decrease in the product of the arteriovenous Pco₂ gradient and CO. The arteriovenous CO₂ content difference, calculated from $\dot{V}CO_2$ and CO (Fick principle), paralleled the arteriovenous Pco₂ difference—both before, during, and after hypoperfusion. As the arteriovenous Pco₂ difference reflects the gradient in CO₂ content (30), the data strongly suggest equilibrium (steady state) between CO₂ output from the tissues and the lungs before, during, and after hypoperfusion. During hypoperfusion, an elevated mixed venous Pco₂ and respiratory acidosis in the tissues are thus caused by a widened arteriovenous CO₂ content gradient due to a greater reduction in tissue blood flow than in CO₂ output.

The widening of the Pco₂ gradient was reversed during reperfusion although $\dot{V}CO_2$ increased above baseline. This was accompanied by a small overshoot in $\dot{V}O_2$ and by a gradual increase in body temperature. The elevated RQ during reperfusion, accompanied by a decrease in lactate and an increase in bicarbonate concentrations, may have been caused in part by oxidation of lactate, which results in regeneration of bicarbonate (31,32). Hence, the greater overshoot in $\dot{V}CO_2$ than in $\dot{V}O_2$ after PEEP indicated increased tissue metabolism after prior ischemia and a slight increase in body temperature rather than washout of CO₂ accumulated during hypoperfusion. We may therefore assume equilibrium between tissue CO₂ production and output. Hence, tissue CO₂ production decreased during

ischemia and the elevated arteriovenous gradient in Pco₂ (and pH) was caused by a greater reduction in tissue blood flow than in CO₂ production, so that tissue CO₂ removal was impaired. At constant alveolar ventilation, a decrease in tissue CO₂ production and output would result in a low Pco₂ in arterial blood. However, this was prevented by an increase in V_d/V_t after an increased airway pressure and a decreased pulmonary blood flow during PEEP (13). Conversely, a slightly increased arterial (and mixed venous) Pco₂ during reperfusion was solely caused by increased tissue CO₂ production as alveolar ventilation had returned to baseline values.

Our results seem partly at variance with those of others who observed respiratory alkalosis in arterial blood and respiratory acidosis in mixed venous blood during cardiopulmonary resuscitation in artificially ventilated pigs and humans (6-12). During pericardial tamponade in conscious dogs, mixed venous acid-base balance is almost unchanged, whereas respiratory alkalosis develops in arterial blood (17). In these studies, respiratory acid-base changes predominated, even at increased lactate concentrations, whereas development of metabolic acidosis in arterial and mixed venous blood at almost constant arterial Pco₂ prevailed in our model. In many studies, intravenous administration of sodium bicarbonate, contributing to a high Pco₂ in mixed venous blood (4,6,8), or hyperventilation and respiratory alkalosis in arterial blood (6-12,17), may have confounded the assessment of acid-base changes after a reduction in CO alone and may have obscured metabolic acid-base disturbances (5). The influence of time may also

contribute to the discrepancy of our results with others, as mixed venous respiratory acidosis may develop acutely during hypoperfusion (6-9) and as metabolic acidosis may evolve slowly after accumulation of lactic acid (1,3-5,7,8,13-17). Our results agree with studies on canine hemorrhagic shock in which metabolic acidosis developed in arterial and mixed venous blood, with superimposed respiratory acidosis in the latter (13-16). Coronary artery occlusion in dogs resulted in myocardial acidosis after a decreased bicarbonate concentration and an increased P_{CO_2} , indicating predominant metabolic acidosis with superimposed respiratory acidosis (19).

The blood flow-dependent arteriovenous gradients of P_{CO_2} and pH in this study thus agree with those during other low-flow states (6-18). The mechanisms for these changes are not well understood. A high P_{CO_2} in venous blood and tissue during hypoperfusion has been attributed to increased CO_2 production through bicarbonate buffering of lactic acid even in the absence of metabolic acidosis and of measurement of CO_2 production (10,11,13,15,16,19). Our results indicate that increased tissue P_{CO_2} during hypoperfusion cannot be simply explained by bicarbonate buffering of organic acids and by increased CO_2 production. During physical exercise, an increase in lactate results in an equivalent decrease in bicarbonate and a greater increase in $\dot{V}CO_2$ than in $\dot{V}O_2$ (31-33). Although $\dot{V}CO_2$ decreased, an increased RQ may well be the result of buffering in our model (33). The buffering of lactic acid could only partly explain the decrease in bicarbonate during hemorrhagic shock and coronary ischemia in the dog (14,16,19). Our results agree with these observations, so that bicarbonate buffering of lactic acid could only partly explain the increased RQ during hypoperfusion. Buffering of organic acids other than lactic acid, released during ischemia, anaerobic decarboxylation reactions, and preferential oxidation of carbohydrates including lactate in tissues with maintained oxidative capacity such as the heart, may have contributed to the elevated RQ (31,34).

A low F_{ECO_2} during hypoperfusion in our model was caused by decreased tissue CO_2 production and not by diminished pulmonary blood flow and increased dead-space ventilation. This argues against the suggestion by others that a high venous P_{CO_2} , a low end-tidal CO_2 tension, and a positive relation of the latter with blood flow are caused by flow-dependent decreases in CO_2 excretion by the lungs during hypoperfusion (6,7,9-11,17,18,20-22). Blood flow-dependent CO_2 production would also explain the relation of arterial P_{CO_2} to blood flow (at a given alveolar ventilation) during cardiopulmonary resuscitation as found by others (22). The overshoot in end-tidal CO_2 tension after successful cardiopulmo-

nary resuscitation has been explained by washout of CO_2 accumulated during hypoperfusion (9,10,20-22). Our results, however, suggest that this overshoot can be partly explained by increased CO_2 production after reperfusion.

Widening of the arteriovenous P_{CO_2} gradient during hypoperfusion may depend on hyperventilation and a decrease in arterial P_{CO_2} (8,10,17). Our results are not consistent with this idea, and the lack of a gradient during combined cardiorespiratory arrest (8,10) could be explained by a severely diminished tissue CO_2 production. Conversely, alveolar hyperventilation would limit the increase in tissue P_{CO_2} and would ameliorate tissue acidosis during ischemia: a decreased arterial P_{CO_2} would lead to a decreased mixed venous P_{CO_2} and to an increased pH, if blood flow, CO_2 production, and thus the arteriovenous P_{CO_2} gradient are unchanged, as can be inferred from other studies also (15,17). Intravenously administered sodium bicarbonate increases CO_2 production, and this could aggravate intracellular acidosis as CO_2 crosses cell membranes more rapidly than the bicarbonate ion (35). As our results indicate that the increased mixed venous P_{CO_2} during hypoperfusion is not caused by increased CO_2 production or by impaired CO_2 excretion by the lungs, a bicarbonate-induced increase in CO_2 production in mixed venous blood may only result in a paradoxical decrease in intracellular pH (at a given blood flow) if accompanied by an increase in arterial P_{CO_2} not prevented by hyperventilation (4). Hence, the argument that increased CO_2 production, mixed venous respiratory acidosis, and impaired pulmonary CO_2 excretion should preclude treatment of metabolic acidosis with bicarbonate during hypoperfusion (3,4,6-12,17,18,20-22) seems not true.

The recommendation to assess the acid-base state in the tissues from venous and not from arterial blood because of elevated P_{CO_2} and pH gradients (6-8,10,17) is only partly valid, because the reduction in $st.[HCO_3^-]$ concentration in arterial blood equals that in mixed venous blood during hypoperfusion. Analyses of arterial blood could thus guide alkali therapy of (severe) metabolic acidosis to ameliorate the detrimental effect of acidosis on the heart (35-37). This is of practical importance because arterial blood is usually easier to obtain than mixed venous blood. Nevertheless, analysis of mixed venous blood is superior for judging tissue oxygenation; the decrease in mixed venous SO_2 is greater than the modest changes in acid-base balance during ischemia.

In conclusion, ischemia after incremental PEEP results in metabolic acidosis with superimposed respiratory acidosis. This is not caused by increased production or by impaired pulmonary excretion of CO_2 but by a greater decrease in tissue blood flow

than in CO_2 production, so that CO_2 stores in the body increase. Decreased pulmonary blood flow and increased dead-space ventilation prevent a decrease in arterial Pco_2 by diminished CO_2 production. A smaller reduction in CO_2 production than in O_2 uptake is only partly explained by bicarbonate buffering of lactic acid.

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Halothane Attenuates Small Arteriole Vasodilation to Serotonin (5-HT) in Skeletal Muscle

Eleanor F. Asher, MD, Nancy L. Alsip, PhD, Ping Y. Zhang, MD, and Patrick D. Harris, PhD

Departments of Anesthesia and Physiology, School of Medicine, and The Center for Applied Microcirculatory Research, University of Louisville, Louisville, Kentucky

Inhaled anesthetics may have an effect on the microcirculation through selective alteration of receptor-mediated control. Halothane was chosen because its actions in the microcirculation have been determined previously. Serotonin has received recent attention as a potential mediator of vascular changes in a number of disease states. We obtained concentration-response curves for serotonin-induced constriction of large arterioles and dilation of small arterioles ($<60\ \mu\text{m}$ diameter) in the cremaster muscle of halothane-anesthetized and decerebrate rats. Cre-

master muscles were prepared for microscopic viewing, leaving the neural and vascular supply intact. Serotonin concentration-response curves were obtained before and after receptor antagonist application. Large arteriole constriction was not affected by halothane. Dilation of small arterioles was decreased in halothane-anesthetized animals but enhanced in the presence of methysergide, a nonspecific antagonist. These data indicate that halothane interferes with occupancy of 5-hydroxytryptamine receptors.

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Although it is known that volatile inhaled anesthetics act in the central nervous system to produce reversible changes in neurologic function, the exact mechanisms by which these agents inhibit synaptic transmission are not known. Many theories of anesthetic action have been postulated, including the Meyer-Overton hypothesis; membrane expansion or disorder, and various lipid or protein interactions (1,2). Ultimately, whatever the mechanism, the most probable site of action lies in the cell membrane. Although the anesthetic action of the inhaled anesthetics results from disruption in the neuronal membrane, significantly documented alterations of membrane function are not confined to the cell membranes of the central nervous system but are tissue-nonspecific. It is probable that many or all tissues are affected including cell membranes of vascular smooth muscle.

The cell membrane is the site of receptors that act through second messenger systems (G proteins) that lie within the membrane and trigger intracellular events. Therefore, changes in membrane fluidity could influence receptor binding, coupling of the

receptor and second messenger system, and transmission of the second messenger to the effector site. It is known that some inhaled anesthetics can alter interactions between muscarinic acetylcholine receptors and G proteins in rat brainstem (2,3).

In humans, halothane, enflurane, and isoflurane have similar cardiovascular effects, although the magnitude of these effects is dose-dependent. This similarity of effect was also shown in rats by Seyde and Longnecker (4) who further demonstrated that regional blood flow distribution was similar in most organ systems of rats anesthetized with any one of these three anesthetics. Previous studies of the microcirculation involved halothane and several other anesthetics that are no longer used clinically (diethyl ether, cyclopropane, and methoxyflurane). Generalized small artery and vein dilation was demonstrated in response to halothane in a variety of vascular beds (5). However, no data have been reported previously on anesthetic modification of receptor control of vascular smooth muscle.

We elected to use halothane as a prototype of an inhaled anesthetic in our study. Even though its clinical use is less common than enflurane or isoflurane, it is still included in clinical practice in the United States and is frequently used in other countries. More importantly, of these inhaled anesthetics, halothane is the only one whose actions in the microcirculation have been previously studied.

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Address correspondence to Dr. Asher, Department of Anesthesiology, School of Medicine, University of Louisville, Louisville, KY 40292.

To study the microcirculation of sensitive deep tissues, it is necessary to use an anesthetic. This creates a dilemma in attempting to compare the anesthetic influence on the vessels versus their status in an awake state. We used decerebrate rats as a control group to alleviate this problem. Transection of the brainstem at the midcollicular level produces neurosurgical anesthesia and negates the use of anesthetic drugs and their potential cardiovascular or microvascular interactions. This preparation most closely approximates the regional hemodynamic status of an awake rat (6) and is specifically recommended for in vivo skeletal muscle microvascular studies. Not only are the obvious complications of anesthesia avoided, but arteriolar tone and vasomotion are preserved in the skeletal muscle microcirculation (7).

Recently, attention has focused on the clinical importance of serotonin (5-hydroxytryptamine, 5-HT). Serotonin may play an important role in hypertension (8-12) and in a variety of vascular diseases including intermittent claudication (13), preeclampsia (14), Raynaud's phenomenon (15), and carcinoid syndrome (16). The recent development of potent and selective serotonergic antagonists has spurred research in this area to further define serotonin's role in cardiovascular control mechanisms (17).

Serotonin has unique microvascular effects. This amine can constrict or dilate blood vessels. In the cremasteric (18), pial (19), and coronary (20) microvasculature, serotonin constricts larger distributing arterioles but dilates small precapillary arterioles. In the cremaster muscle, serotonin acts on separate 5-HT receptors to cause constriction (5-HT₂ receptors) or dilation (5-HT₁-like receptors) (21). Because of the dual actions of serotonin, both constrictor and dilator mechanisms can be studied simultaneously. Our purpose was to determine whether halothane altered receptor control of the microcirculation by serotonin. Serotonin was used in this study because it has potential clinical relevance and its actions in the skeletal muscle microvasculature have been well defined.

Methods

Male Sprague-Dawley rats were purchased as weanlings (50-75 g) and were caged individually in a room that was temperature and humidity controlled with a 12-h light/12-h dark cycle. They were fed standard laboratory rat diet with access to tap water ad libitum until body weight reached 140-160 g (~14-18 days after weaning or 5-6 wk of age). All protocols were approved before the study by the University of Louisville Institutional Animal Care and Use Committee.

On the day of an acute experiment, a rat was decerebrated or anesthetized with halothane as described below.

Decerebration

These animals were initially anesthetized (intraperitoneally) with urethane (800 mg/kg) and α -chloralose (60 mg/kg). Decerebration was done according to the technique of Faber et al. (7). The head of the rat was placed in a Kopf stereotaxic instrument, the cranium was exposed, and a bilateral parietal craniotomy was performed with a power-driven No. 8 dental burr. The exposed dura mater was cut with care to avoid the large meningeal vessels and the midsagittal sinus, which could lead to blood loss and air emboli. A micromanipulator with a custom-designed knife blade was used to transect the brain at a calculated distance (approximately 3.0 mm for a 150-g rat) posterior to bregma without section of the midsagittal sinus or of the large vessels at the base of the midbrain (posterior cerebral and communicating arteries). Periosteal and bone hemorrhage was slight and was arrested with a ferric subsulfate solution. This approach minimizes total blood loss to less than 0.5 mL. Subsequently, all animals received 2 mL of saline solution subcutaneously as replacement for any evaporative and bladder fluid loss during the experiment.

The craniotomy was closed with Gelfoam (Upjohn) and Stickywax (Englehard) after verification of minimal brain swelling at the lesion site. The cut skin margins and periosteum were covered with xylocaine hydrochloride (2%, Lidocaine jelly), and the scalp wound was closed.

Halothane

The animal was placed in a 4-L sealable plastic container with an inlet and outlet port on opposite ends. The inlet port was connected to a halothane vaporizer (Fluotec, Cyprane Ltd., U.K.). The outlet port was connected to a low-level suction exhaust (to prevent contamination of the laboratory with halothane). Compressed air at a 1-L/min flow was directed through the vaporizer and was regulated by a flow meter. Halothane concentration was continuously monitored by a Puritan-Bennett Anesthetic Agent Monitor 222 (Datex, Puritan-Bennett Corp., Kansas City, Mo.), which was positioned between the vaporizer and the animal. For anesthetic induction of the animal within the container, halothane concentration was maintained at 2.5% for 60 \pm 10 s, at which time the animal lost the righting reflex. The anesthetized animal was then removed from the bottle, and the face of the rat was covered by a

snug-fitting mask that was connected to the vaporizer and suction exhaust. The right carotid artery was cannulated and a tracheostomy was performed. The mask was removed and the vaporizer and suction exhaust were connected to the tracheostomy tube via a T-tube. The cremaster muscle was surgically prepared for microscopy. During these surgical procedures, the halothane concentration was maintained at 1.2%–1.5%, which prevented animal movement in response to surgical stimulus. After surgery and for the remainder of the experiment, the inspired halothane concentration was maintained at $0.7\% \pm 0.1\%$.

Cremaster Preparation

In both decerebrate and halothane-anesthetized rats, one carotid artery and the trachea were cannulated to monitor arterial pressure and to maintain a patent airway.

To prepare the cremaster muscle for microscopic observation (7,18), the right scrotal sac was incised and the cremaster-enclosed testicle was gently dissected free of connective tissue. The cremaster muscle was then incised and dissected free of the testicle. This procedure left intact circulation and neural connections to the cremaster.

The testicle was gently pushed into the abdominal cavity. The animal was placed on a plexiglass board, and the cremaster muscle was positioned by sutures over an optical port in the bottom of a 60-mL tissue bath that was attached to the plexiglass board. The bath was filled with a modified Krebs' solution (113 mM NaCl, 11.6 mM dextrose, 4.7 mM KCl, 1.2 mM $\text{MgSO}_4 \cdot 7 \text{H}_2\text{O}$, 1.2 mM KH_2PO_4 , 2.6 mM $\text{CaCl}_2 \cdot 2 \text{H}_2\text{O}$, and 25 mM NaHCO_3). Bath temperature was maintained at $34.5 \pm 0.5^\circ\text{C}$ by an indwelling bath heating unit. Nitrogen and CO_2 gases were bubbled continuously through the cremaster bath to constantly stir the bath, to provide pH control (by CO_2 flow), and to regulate O_2 tension in the bath (by N_2 flow to carry away dissolved O_2). These gas flows were set to maintain bath pH at 7.4 ± 0.05 , oxygen tension at 30–50 mm Hg, and CO_2 tension at 35–40 mm Hg.

Rectal temperature of the animal was monitored and maintained at $37^\circ\text{--}38^\circ\text{C}$ by a heating pad under the animal. The arterial pressure of the animals was continuously monitored, and any animal with a mean arterial pressure lower than 80 mm Hg or with unstable blood pressure was excluded from subsequent data analyses.

The microvessels in the cremaster were viewed at approximately $850\times$ magnification on a video monitor that was part of a calibrated closed-circuit television microscopy system. Inside vessel diameters

were measured with calipers from the monitor screen. The red cell column, which is easily visible, was measured to determine inside vascular diameters. The images were recorded on videotape and subsequently used for verification of diameter measurements.

Microvascular Data

After the decerebration procedure, there was a 3–4-h animal stabilization period to dissipate the cardiovascular effects of the anesthetic through metabolism (7). After preparation of the cremaster muscle for microscopy in both the halothane-anesthetized and decerebrate animals, there was a cremaster stabilization period of 30–60 min. During this period, all variables were monitored to ensure stable values, and microvessels were selected for observation.

In all experiments, vessel diameters were measured for the major large arteriole and vein pair (A1 and V1, respectively) that supply the cremaster and for smaller arterioles (A3) that had spontaneous vasomotion (rhythmical cycles of partial vasoconstriction and vasodilation). These A3 vessels were selected from the same general area of the cremaster muscle for each animal. Microvascular images were recorded on videotape for later measurements of vessel diameter and A3 vasomotion at 1-min intervals.

Protocol for Serotonin Dose-Response Curves

After the cremaster stabilization period, there was a 20-min baseline period. Vessel diameters and frequency of vasomotion were measured at 1-min intervals during the last 10 min of this period. Then 5-HT (serotonin) was added directly to the cremaster bath to give a 5-HT concentration in the bath of 1×10^{-9} M, which remained in the bath for 10 min. The concentration of 5-HT in the bath was increased in 10-fold increments (with 10 min at each concentration) until the last 5-HT concentration in the bath was 1×10^{-4} M. After this 5-HT concentration, the cremaster bath was drained and refilled repeatedly with fresh Krebs' solution to wash out the serotonin. Vessel diameters and vasomotion were measured at 1-min intervals during each 10-min 5-HT period. Vessel diameters were measured at 5-min intervals during the washout period.

Once the vessels had returned to within 5% of their baseline diameters, one of the 5-HT antagonists (methysergide for blockade of both 5-HT₁ and 5-HT₂ receptors, or LY53857 for specific blockade of the 5-HT₂ receptor only) was added to the cremaster bath, and this antagonist remained in the bath for the remainder of the experiment. After the antagonist

had been in the bath for 20 min, vessel diameters and vasomotion were measured at 1-min intervals for an additional 10 min; then, a full 5-HT concentration-response curve over the 10^{-9} – 10^{-4} M range was repeated in the presence of the antagonist. No antagonist was added for the second concentration-response curve in the control groups. After the highest dose of 5-HT had been added in the second dose-response curve of all groups, the non-specific vasodilator papaverine (10^{-5} M) was added to the cremaster bath to assess the dilator capacity of the vessels.

Data Analyses

Log concentration-response curves were obtained for both the large A1 and small A3 arterioles. As the maximal constriction for the A1 arterioles was not obtained, the data for the A1 diameters were expressed as percent changes from baseline.

There was wide variability among the A3 baseline diameters because these vessels had different levels of basal sympathetic tone; therefore, the A3 data at each dose were expressed as a percent of maximal dilation capacity by the following formula:

Dilator capacity at dose (%) =

$$\frac{(\text{Vessel diameter at dose } x) - (\text{Baseline diameter})}{(\text{Maximal diameter with papaverine}) - (\text{Baseline diameter})} \times 100.$$

The ED_{50} values for the responses of the A3 arterioles were calculated by a probit analysis. The ED_{50} values could not be obtained for the A1 responses as maximal A1 constriction was not obtained. ED_{50} values were converted to pD_2 values ($pD_2 = -\log ED_{50}$), which measure microvascular sensitivity to 5-HT.

Comparisons among the treatment groups were made by one-way analysis of variance, using the Bonferroni procedure for multiple comparisons (22). For any comparison of only two groups, an unpaired *t*-test was applied to the data. The statistical significance level was $P < 0.05$. All data values are reported as the mean \pm SEM.

Results

Six groups of animals were studied: (a) seven decerebrate control animals with two 5-HT concentration-response curves but no antagonist; (b) 11 decerebrate-methysergide animals that had a 5-HT concentration-response curve followed by a second 5-HT concentration-response curve with methysergide in the cremaster bath; (c) eight decerebrate LY53857 animals that had a 5-HT concentration-response curve followed by a second 5-HT concen-

Table 1. Baseline Mean Arterial Blood Pressure

	Baseline MAP	
	Decerebrate (mm Hg)	Halothane (mm Hg)
Control	111 \pm 4.3 (<i>n</i> = 7)	79 \pm 1.9 ^a (<i>n</i> = 7)
Methysergide	104 \pm 3.2 (<i>n</i> = 11)	90 \pm 4.0 ^a (<i>n</i> = 7)
LY53857	109 \pm 2.2 (<i>n</i> = 8)	93 \pm 4.2 ^a (<i>n</i> = 10)

MAP, mean arterial blood pressure.

^aHalothane significantly ($P < 0.05$) differs from decerebrate.

Table 2. A1 Baseline Diameters

	Diameter	
	Decerebrate (μ m)	Halothane (μ m)
Control	105 \pm 7.0	90 \pm 2.0
Methysergide	114 \pm 6.7	89 \pm 8.6
LY53857	97 \pm 8.4	105 \pm 6.0

tration-response curve with LY53857 in the cremaster bath; (d) seven halothane control animals with two 5-HT concentration-response curves but no antagonists; (e) seven halothane-methysergide animals that had a 5-HT concentration-response curve followed by a second 5-HT concentration-response curve with methysergide in the cremaster bath; and (f) 10 halothane-LY53857 animals that had a 5-HT concentration-response curve followed by a second 5-HT concentration-response curve with LY53857 in the cremaster bath.

Mean arterial pressures in the halothane-anesthetized animals were significantly less during the pre-serotonin baseline period than in the decerebrate groups (Table 1). Yet, the large distributing A1 arterioles had similar baseline diameters in the halothane-anesthetized and decerebrate groups (Table 2). Likewise, the small precapillary A3 arterioles had similar baseline diameters for comparison of the halothane and decerebrate groups (Table 3). The only significant differences were the A3 diameters in the halothane-anesthetized group in the presence of LY53857. Although the absolute values were smaller in this group, the dilator capacity was not different from that of any of the other groups. Thus, the data analysis was not affected.

Serotonin produced a dose-dependent contraction of the large distributing A1 arterioles in the cremaster muscle, and the magnitude of this contraction was similar in both the halothane-anesthetized and decerebrate animals (Figure 1) at all serotonin concentrations (except for 10^{-6} M). Methysergide, a nonspe-

Table 3. A3 Baseline and Maximal Diameters

	Baseline		Maximal	
	Decerebrate (μm)	Halothane (μm)	Decerebrate (μm)	Halothane (μm)
Control	11.7 \pm 1.16	12.7 \pm 1.38	25.6 \pm 2.21	19.8 \pm 0.94
Methysergide	8.9 \pm 0.73	9.6 \pm 1.07	21.1 \pm 1.06	19.4 \pm 1.31
LY53857	10.3 \pm 0.97	8.4 \pm 0.48 ^a	23.3 \pm 1.49	17.9 \pm 1.09 ^b

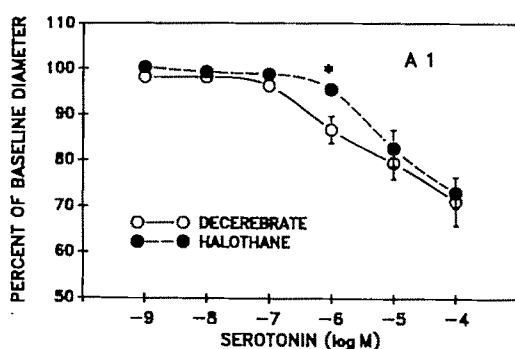
^aSignificantly ($P < 0.05$) differs from halothane control.^bHalothane significantly ($P < 0.05$) differs from decerebrate.

Figure 1. The control concentration-response curves to 5-HT in large distributing arterioles (A1) in the decerebrate (open circles) and halothane-anesthetized (filled circles) groups. The ordinate gives data as percent of baseline diameter, where values less than 100% indicate constriction. Asterisks indicate a significant ($P < 0.05$) difference between the groups at that concentration.

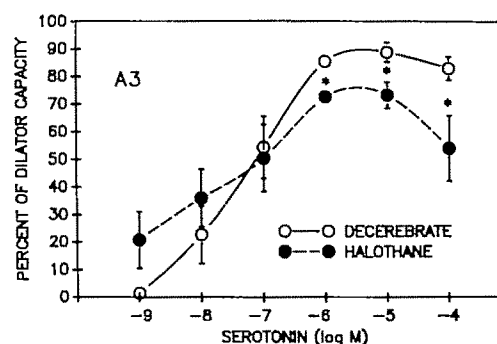


Figure 2. The control concentration-response curves to 5-HT in small precapillary arterioles (A3) in the decerebrate (open circles) and halothane-anesthetized (filled circles) groups. The ordinate gives data as percent of the dilator capacity (see text for details), where values greater than zero indicate dilation. Asterisks indicate a significant ($P < 0.05$) difference between groups at that concentration.

cific antagonist of serotonin receptors, completely blocked this serotonin-induced contraction of large A1 arterioles in both animal groups (data not shown). Likewise, a specific antagonist of the 5-HT₂ receptor subtype also blocked the serotonin-induced contraction of A1 (data not shown) in both the halothane-anesthetized and decerebrate animal groups.

In contrast to the constriction of the large A1 arterioles, serotonin produced a dose-dependent dilation of the small precapillary A3 arterioles in the cremaster muscle, but the magnitude of this dilation was somewhat smaller at the higher (10^{-6} through 10^{-4}) serotonin concentrations in the halothane-anesthetized animals (Figure 2). Methysergide blocked this serotonin-induced dilation of small A3 arterioles for all but the highest (10^{-4} M) concentration of serotonin in the decerebrate animals (Figure 3). Methysergide also blunted the serotonin-induced dilation of small A3 arterioles in the halothane-anesthetized animals, but the small precapillary A3 arterioles in these animals still exhibited a significant dilation for all but the lowest (10^{-9}) serotonin concentration (Figure 3).

The specific 5-HT₂ receptor antagonist (LY53857) did not have any significant effect on the dose-dependent serotonin-induced dilation of small pre-

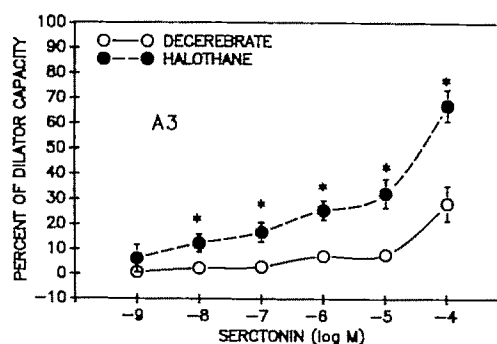


Figure 3. The concentration-response curves to 5-HT in small precapillary arterioles (A3) during the presence of methysergide (a 5-HT₁ and 5-HT₂ antagonist) in the decerebrate (open circles) and halothane-anesthetized (filled circles) groups. The ordinate gives data as percent of the dilator capacity (see text for details), where values greater than zero indicate dilation. Asterisks indicate a significant ($P < 0.05$) difference between the groups at that concentration.

capillary A3 arterioles in the decerebrate animals (data not shown) at the 10^{-7} concentration or in the halothane-anesthetized animals (data not shown).

Calculations of pD₂ values (from the agonist concentrations that give half-maximal dilations) provide a well-accepted approach to determine receptor reac-

Table 4. Serotonin pD_2 Values for Dilation of Third-Order Arterioles

	pD_2 Values	
	Decerebrate	Halothane
Control	7.36 ± 0.268	7.99 ± 0.427
Methysergide	$<4.00^a$	5.48 ± 0.403^b
LY53857	6.93 ± 0.308	7.72 ± 0.480

^aThe response to serotonin did not reach a 50% dilation even at the highest concentration of 10^{-6} M.

^bHalothane-methysergide significantly ($P < 0.05$) differs from decerebrate-methysergide.

^cStatistically significant ($P < 0.05$) difference between groups.

tivity to specific agonists. The pD_2 values for small A3 arteriole reactivity to serotonin were similar in the decerebrate and halothane-anesthetized animals (control in Table 4), and the specific 5-HT₂ receptor antagonist (LY53857) had no significant effect on A3 reactivity to serotonin in either group (Table 4). Methysergide, a nonspecific 5-HT receptor antagonist significantly reduced serotonin receptor reactivity in small A3 arterioles of both decerebrate and halothane-anesthetized rats (Table 4). But small A3 arteriole reactivity (pD_2) to serotonin was significantly greater in the halothane-anesthetized animals than in the decerebrate animals during the presence of the serotonin receptor antagonist methysergide (Table 4).

Discussion

The mechanisms by which general anesthetics selectively influence the microcirculation of some organ systems have not been studied extensively, yet it is these microcirculatory mechanisms that determine nutrient blood flow and O₂ delivery to cellular systems. The vasoactive amine serotonin, which gives differential effects in the microcirculation through actions on several 5-HT receptor subtypes (21), was the subject of recent clinical interest because of its potential causative linkage to a number of hypertensive disorders (17). In our study, serotonin produced a dose-dependent contraction of the large distributing A1 arterioles, and this concentration-response curve was similar in the halothane-anesthetized and decerebrate animals. Both methysergide, a 5-HT₁ and 5-HT₂ serotonin receptor antagonist, and LY53857, a specific 5-HT₂ receptor antagonist, blocked the serotonin-induced contraction of these A1 arterioles in both animal groups. Thus, halothane does not appear to alter the 5-HT₂ receptor control of the microvasculature, at least not in skeletal muscle.

Halothane, however, appears to alter the 5-HT₁ receptor-mediated response in the small A3 arteri-

oles. At serotonin concentrations of 10^{-6} M and greater, the A3 arterioles of our halothane-anesthetized animals dilated significantly less than those of decerebrate animals. In contrast, the halothane group demonstrated significantly more dilation than the decerebrate group when methysergide was present. These results could represent an action of halothane to reduce the binding of agonists (such as serotonin) and antagonists (such as methysergide) to the 5-HT₁ receptor.

As an alternative explanation, the reduced serotonin-induced A3 dilation in halothane-anesthetized rats could reflect an action of halothane to reduce the release of endothelium-derived relaxing factor (EDRF), a substance that is thought to alter microvascular reactivity to several agonists (23,24). Serotonin dilates large veins and arteries through the release of EDRF from endothelial cells (25,26), and this serotonin-induced EDRF release is dependent on calcium (27,28), at least in some tissues. Malancinico et al. (29) have demonstrated that halothane decreases the fast component of cellular calcium uptake. The decrease in serotonin-induced dilation of small A3 arterioles in the halothane-anesthetized animals of our study could reflect an inhibition of EDRF release through halothane depression of the mechanisms that control the fast component of cellular calcium uptake. Other data also support indirectly the idea that halothane reduces EDRF release. Decreased release of EDRF occurs in hypertensive rats (30), and halothane anesthesia markedly decreases regional blood flow to several organs in hypertensive rats (31). On the other hand, unlike large arteries and veins, serotonin-induced dilation of small arterioles in striated muscle is not mediated by EDRF (32); thus, the action of halothane to reduce serotonin-induced dilation of small arterioles cannot be solely an action of halothane to reduce EDRF release.

Serotonin plays a role in differential vascular control mechanisms in the microcirculation and some of these serotonin mechanisms are altered by halothane. It now seems likely that anesthetics may selectively alter different microvascular mechanisms to give vastly different microcirculatory perfusion patterns in some organ systems during anesthesia. Thus, anesthetic modulation of hormonal control in the microcirculation of different organ systems merits more research attention to identify new criteria for anesthetic selection in patients whose peripheral vasculature is altered by disease states or shock of traumatic, septic, or cardiogenic origin.

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Effects of Augmenting Cardiac Contractility, Preload, and Heart Rate on Cardiac Output During Enflurane Anesthesia

Michiko Sato, MD, Sumio Hoka, MD, Hiroyuki Arimura, MD, Kyoichi Ono, MD, and Junichi Yoshitake, MD

Department of Anesthesiology and Critical Care Medicine, Faculty of Medicine, Kyushu University, Fukuoka, Japan

Changes in cardiac output in response to augmenting cardiac contractility, preload, and heart rate during enflurane anesthesia were examined in 12 open-chested dogs. Cardiac contractility was assessed by the slope of the end-systolic pressure-volume relation (E_{\max}). Dobutamine (3, 6, and 9 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was administered to augment cardiac contractility. Autologous blood (5.0 and 10 mL/kg) was infused to increase preload. Atrial pacing was used to increase the heart rate by about 30%. Cardiac output decreased from 96 ± 4 (0% enflurane) (mean \pm SE) to 73 ± 5 (1.7% enflurane) and to 46 ± 7 mL $\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ (3.4% enflurane), concomitantly with decreases in E_{\max} from 6.0 ± 1.2 (0% enflurane) to 4.5 ± 1.2 (1.7% enflurane) and to 2.5 ± 0.5 mm Hg/mL (3.4% enflurane). Dobutamine (3, 6, and 9 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) increased E_{\max} from $69\% \pm 7\%$ (compared to 0% enflurane with no dobutamine) to $139\% \pm 15\%$, $167\% \pm 25\%$, and $183\% \pm 35\%$ at 1.7% enflurane, and from $43\% \pm 8\%$ to $78\% \pm 7\%$, $137\% \pm 20\%$, and $157\% \pm 22\%$ at 3.4% enflurane, respectively. The decreases in cardiac output by 1.7% and 3.4% enflurane were reversed by the intravenous administration of 3 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ of dobutamine. Cardiac output was significantly increased by administration of 10 mL/kg of autologous blood at 1.7% enflurane, but did not significantly increase at 3.4% enflurane. Increasing the heart rate did not significantly increase cardiac output at 1.7% and 3.4% enflurane. The results of this study suggest that increasing cardiac contractility is the most effective therapeutic means of reversing circulatory depression during enflurane anesthesia.

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Although the causes and mechanisms of enflurane-induced circulatory depression have been studied, there are few reports that examine methods to counteract enflurane-induced circulatory depression (1-8). We sought to find an appropriate use of therapeutic means to counteract enflurane-induced decreases in cardiac output. Cardiac output (CO) is the product of stroke volume and heart rate (HR), and the former is determined by preload, afterload, and cardiac contractility (9). We therefore examined the effect of selective augmentation of cardiac contractility, preload, and HR on CO and hence on the hemodynamics during enflurane anesthesia. Reducing afterload was not examined, as a reduction of systemic vascular resistance causes further decrease in systemic arterial blood pressure during enflurane anesthesia.

Cardiac contractility has often been investigated by the use of indices that are easily influenced by load-

ing conditions, such as maximum dP/dt, ejection fraction, or systolic shortening of the free wall (10,11). As both preload and afterload are likely to change during enflurane anesthesia, such indices would not properly reflect the changes in cardiac contractility. The slope of the end-systolic pressure-volume relation (E_{\max}) is sensitive to the contractile state of the myocardium but relatively independent of loading conditions (12-15). Therefore, we used E_{\max} as an index of cardiac contractility.

Methods

General Preparation

Experiments were performed on 12 mongrel dogs with body weights ranging from 10 to 16 kg. This study was approved by our institutional animal investigation committee. Anesthesia was induced with thiopental (20 mg/kg) and maintained with an infusion of α -chloralose (10 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$). α -Chloralose was used for basal anesthesia because it has a minor effect on hemodynamics (16). The trachea was intubated, and constant-volume intermittent positive-

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Address correspondence to Dr. Hoka, Department of Anesthesiology, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan.

pressure ventilation at a rate of 14 breaths/min with a mixture of oxygen and nitrogen was instituted to produce normocapnia and to keep arterial oxygen tension at approximately 150 mm Hg. Arterial blood pressure was measured by means of a catheter placed in the aorta through the right axillary artery. This catheter was connected to a Statham pressure transducer (P23ID). A catheter was placed in the superior vena cava through the jugular vein for infusion of drugs. Another catheter was placed in the inferior vena cava through the femoral vein for administration of fluid and withdrawal of blood. Autologous blood (10 mL/kg) was withdrawn into a heparinized container, and 10 mL/kg of dextran was simultaneously infused to replace the withdrawn blood. The electrocardiogram (lead II) was monitored continuously. Body temperature was maintained between 37 and 38°C by external warming.

The chest was opened through a median sternotomy. The pericardium was cut open, and the heart was suspended in a pericardial cradle. A 10- to 14-mm electromagnetic flow probe (FR, Nihon Kohden, Japan) was placed on the ascending aorta, and aortic blood flow was measured with a flow meter (MFV-2100, Nihon Kohden). Left ventricular pressure was measured by a catheter-tipped high-fidelity micromanometer (MPC-500, 7F; Millar Instruments, Houston, Tex.) inserted through the left ventricular apex. Pacing electrodes were sutured to the right atrial appendage. A constant-current stimulator (external pacemaker 202; Cynergy, Wash.) was used for atrial pacing. Arterial blood pressure, left ventricular blood pressure, left ventricular end-diastolic pressure (LVEDP), electrocardiogram, dp/dt of left ventricular pressure, and aortic blood flow were recorded on an eight-channel chart recorder.

Aortic Occlusion

We used an aortic occlusion method to obtain the slope of the end-systolic pressure-volume relation line described by Igarashi and Suga (17). The ascending aorta between the flow probe and the brachiocephalic artery was abruptly occluded with vascular forceps in diastole following steady-state ejecting contractions to produce an isovolumic contraction. The contraction was considered to be isovolumic when it was associated with (a) no ejection in the aortic flow, (b) a monotonic decrease of the aortic pressure, and (c) a smooth sinusoidal left ventricular pressure contour as shown in Figure 1. Each aortic occlusion was performed when left ventricular pressure and aortic flow tracings of ejecting contractions reached steady state at about 10 s after the respirator was stopped in the expiratory phase.

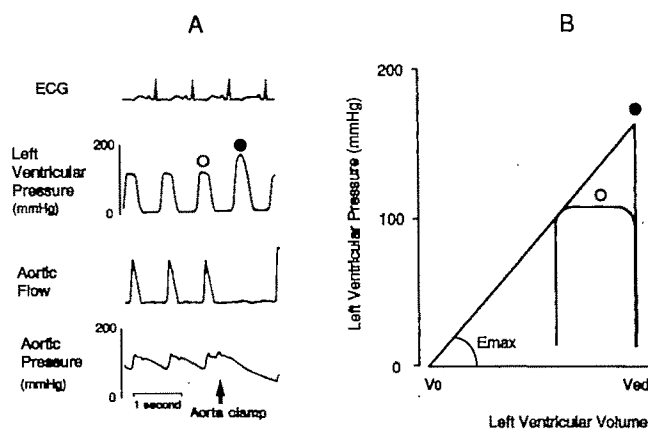


Figure 1. Measurement of E_{max} . (A) Representative recordings displaying the measurement of E_{max} . The aorta was clamped in diastole after ejecting contraction, which produces two beats with the same preload (ejecting [open circle] and isovolumic [closed circle]). Successful aortic clamping is ascertained by the lack of simultaneous elevation of arterial pressure or arterial flow. (B) Schematic diagram of E_{max} . The pressure-volume loop of two beats (open and closed circles) can be drawn as shown in the figure. Connecting the isovolumic peak pressure point with the upper left corner of the ejecting loop gives E_{max} . ECG, electrocardiogram; V_{ed} , end-diastolic volume; V_0 , volume axis intercept of end-systolic pressure-volume relationship.

Data Acquisition

Cardiac output was assessed by aortic blood flow. Stroke volume was obtained by dividing CO by HR, which was an average of 10 beats before aortic occlusion. It was reasonable to assume that the last ejecting contraction and the first isovolumic contraction had the same left ventricular end-diastolic volume in the same contractile state. Therefore, we superimposed two pressure-volume trajectories of the ejecting and isovolumic contractions in the same pressure-volume diagram so that their end-diastolic volumes were equalized. We drew a straight line from the peak systolic pressure point of the isovolumic contraction tangential to the left upper corner of the pressure-volume trajectory of the ejecting contraction according to the end systole. We defined this tangential line to represent the end-systolic pressure-volume line and its slope to be E_{max} , because the end-systolic pressure-volume relation line was defined as the line passing through the left upper corners, namely, end-systolic points of the pressure-volume loops of variably loaded contractions in a given constant contractile state. Thus, E_{max} could be determined as the incremental ratio of ventricular pressures to volumes without measuring absolute volume of the left ventricle.

Experimental Protocol

Three series of experiments were designed to alter cardiac contractility, HR, and preload. Dobutamine

Table 1. Hemodynamic Responses to Dobutamine Infusion in Dogs During Enflurane Anesthesia

	Dobutamine ($\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)			
	0	3	6	9
CO ($\text{mL}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)				
0% ENF	96 \pm 4	122 \pm 5 ^a	136 \pm 6 ^a	145 \pm 18 ^a
1.7% ENF	73 \pm 5 ^a	109 \pm 7 ^b	124 \pm 7 ^{a,b}	134 \pm 9 ^{a,b}
3.4% ENF	46 \pm 7 ^a	106 \pm 11 ^b	119 \pm 11 ^{a,b}	134 \pm 13 ^{a,b}
E _{max} (mm Hg/mL)				
0% ENF	6.0 \pm 1.2	9.1 \pm 2.2 ^a	11.1 \pm 2.7 ^a	12.7 \pm 2.5 ^a
1.7% ENF	4.5 \pm 1.2 ^a	7.8 \pm 1.8 ^b	10.0 \pm 2.2 ^{a,b}	11.0 \pm 2.0 ^{a,b}
3.4% ENF	2.5 \pm 0.5 ^a	4.3 \pm 0.7 ^a	7.2 \pm 1.3 ^{a,b}	8.1 \pm 1.3 ^{a,b}
MAP (mm Hg)				
0% ENF	109 \pm 4	137 \pm 6 ^a	141 \pm 6 ^a	141 \pm 7 ^a
1.7% ENF	72 \pm 6 ^a	106 \pm 6 ^b	114 \pm 6 ^b	116 \pm 6 ^b
3.4% ENF	48 \pm 3 ^a	89 \pm 5 ^{a,b}	98 \pm 5 ^{a,b}	102 \pm 5 ^b
HR (beats/min)				
0% ENF	128 \pm 11	142 \pm 12	159 \pm 12 ^a	169 \pm 12 ^a
1.7% ENF	112 \pm 8 ^a	130 \pm 10 ^b	144 \pm 14 ^b	154 \pm 16 ^{a,b}
3.4% ENF	111 \pm 8 ^a	124 \pm 7	133 \pm 10 ^b	140 \pm 12 ^b
LVEDP (mm Hg)				
0% ENF	7.3 \pm 0.5	5.0 \pm 0.5 ^a	4.5 \pm 0.6 ^a	4.8 \pm 0.5 ^a
1.7% ENF	6.0 \pm 0.5	5.0 \pm 0.3 ^a	4.8 \pm 0.3 ^a	4.6 \pm 0.4 ^a
3.4% ENF	6.5 \pm 1.1	6.3 \pm 0.7	5.8 \pm 0.6	5.0 \pm 0.5 ^{a,b}
dP/dt (mm Hg/s)				
0% ENF	2698 \pm 332	5229 \pm 706 ^a	7096 \pm 706 ^a	8300 \pm 581 ^a
1.7% ENF	1536 \pm 166 ^a	4150 \pm 540 ^{a,b}	5312 \pm 581 ^{a,b}	6349 \pm 664 ^{a,b}
3.4% ENF	747 \pm 42 ^a	2615 \pm 332 ^b	3652 \pm 415 ^{a,b}	4399 \pm 374 ^{a,b}
SVR ($\text{mm Hg}\cdot\text{L}^{-1}\cdot\text{min}^{-1}$)				
0% ENF	95 \pm 9	94 \pm 6	86 \pm 6	81 \pm 5
1.7% ENF	82 \pm 13	81 \pm 13	77 \pm 11	72 \pm 10
3.4% ENF	87 \pm 17	70 \pm 11	67 \pm 10	63 \pm 9 ^a

CO, cardiac output; E_{max}, slope of end-systolic pressure-volume relationship; MAP, mean arterial pressure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure; dP/dt, maximal rate of rise of left ventricular blood pressure; SVR, systemic vascular resistance; ENF, enflurane.

^a*P* < 0.05 vs control (0% enflurane, no dobutamine).

^b*P* < 0.05 vs no dobutamine.

(3, 6, and 9 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) was administered to increase cardiac contractility. Atrial pacing was performed to increase the HR by about 30%. Autologous blood (5 and 10 mL/kg) was infused to increase preload. At first, under basal anesthesia (0% enflurane), dobutamine administration was performed (*n* = 12). Then, the animal was anesthetized with 1.7% or 3.4% enflurane. The order was randomized. Twenty minutes were allowed for a steady cardiovascular state to be achieved after each alteration in inspired concentration. At 1.7% and 3.4% enflurane, dobutamine infusion (*n* = 12), volume load (*n* = 7), and atrial pacing (*n* = 7) were challenged. Those interventions were randomized. Aortic occlusion was performed at each challenge during the steady state of hemodynamics. After volume load, the same amount of blood was withdrawn. Enflurane was administered from a Enflurick vaporizer (Murano Medical, Japan). The vaporizer had been calibrated over the appropriate range of concentrations using an anesthesia/respiratory gas monitor (Raman Scattering Gas Monitor, Rascal, Albion Instruments),

and its ability to maintain these concentrations over the time-course of the study was established.

Statistical Analysis

Data are expressed as the mean \pm SEM. The data were analyzed with analyses of variance for repeated measures. Means were compared with Fisher's least significant difference test using StatView (Abacus Concepts, Berkeley, Calif.) software. *P* values of less than 0.05 were considered significant.

Results

Enflurane produced dose-related decreases in CO and E_{max} (Table 1). Cardiac output decreased by 24% and 52% at 1.7% and 3.4% enflurane, respectively. The E_{max} decreased by 31% and 57% at 1.7% and 3.4% enflurane, respectively. The mean arterial blood pressure (MAP), HR, and dP/dt decreased at 1.7% and 3.4% enflurane. Left ventricular end-diastolic

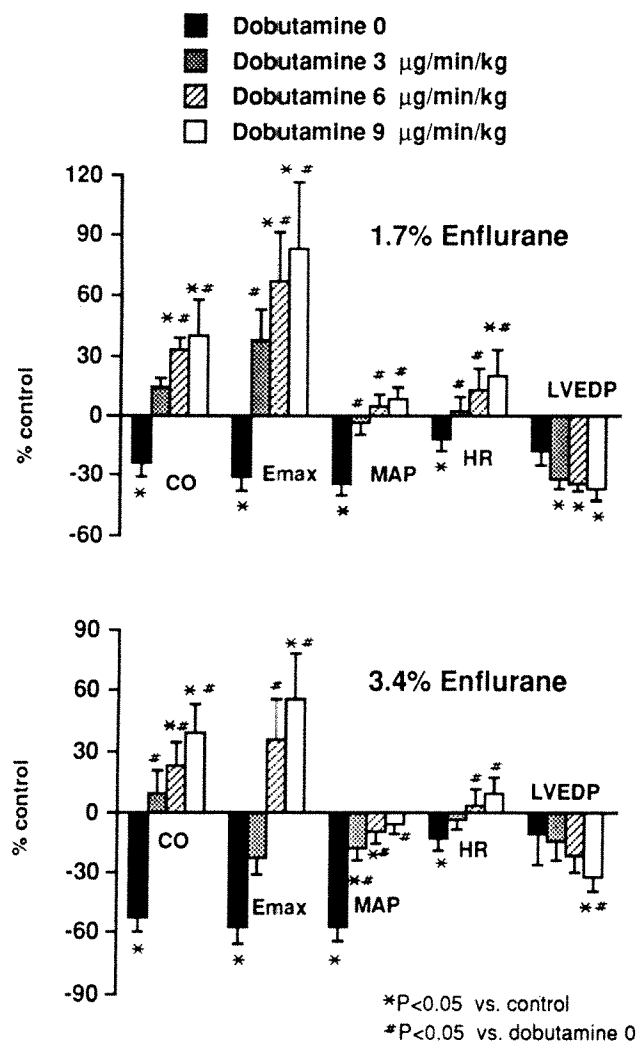


Figure 2. Effects of dobutamine infusion on hemodynamics during 1.7% and 3.4% enflurane. % Control, percent changes from control (0% enflurane and no dobutamine); CO, cardiac output; E_{max} , slope of end-systolic pressure-volume relationship; MAP, mean arterial pressure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure.

pressure and systemic vascular resistance were not significantly changed by enflurane.

Dobutamine produced increases in CO, E_{max} , MAP, HR, and dP/dt at two anesthetic levels. Left ventricular end-diastolic pressure decreased during dobutamine infusion (Table 1). Dobutamine did not significantly change systemic vascular resistance. Figure 2 shows percent changes in CO, E_{max} , MAP, HR, and LVEDP from control values (0% enflurane, dobutamine 0) in response to dobutamine infusion at 1.7% and 3.4% enflurane. The decreases in CO produced by 1.7% and 3.4% enflurane were reversed by $3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ of dobutamine concomitantly with the increases of E_{max} .

The preload was increased by volume loads of 5

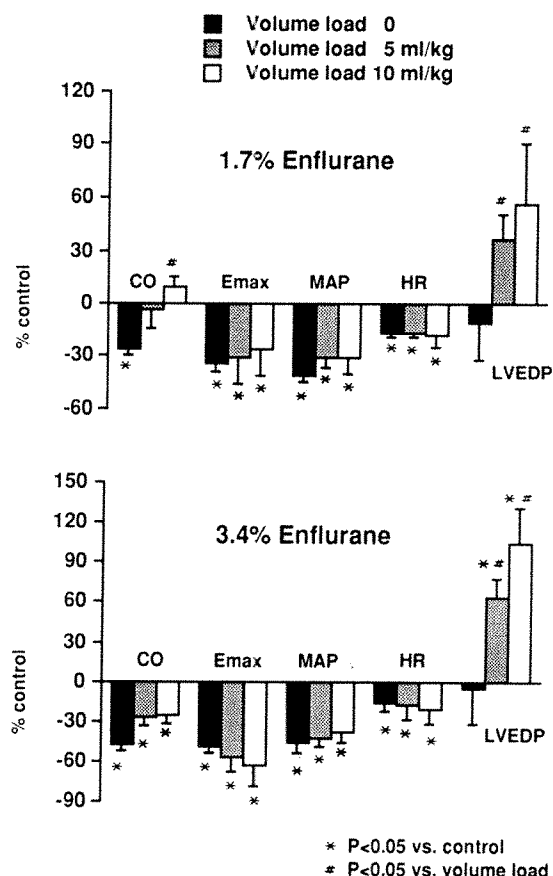


Figure 3. Effects of changes in preload on hemodynamics during 1.7% and 3.4% enflurane. % Control, percent changes from control (0% enflurane); CO, cardiac output; E_{max} , slope of end-systolic pressure-volume relationship; MAP, mean arterial pressure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure.

and 10 mL/kg. Figure 3 shows percent changes in CO, E_{max} , MAP, HR, and LVEDP from control values (0% enflurane) in response to volume load at 1.7% and 3.4% enflurane. The volume load increased LVEDP from 7.0 ± 1.0 to 10.0 ± 1.2 mm Hg (5 mL/kg) and 11.7 ± 1.3 mm Hg (10 mL/kg) at 1.7% enflurane, and from 8.0 ± 1.2 to 12.7 ± 1.0 mm Hg (5 mL/kg) and 15.3 ± 1.4 mm Hg (10 mL/kg) at 3.4% enflurane. Mean arterial blood pressure, E_{max} , and HR were not significantly changed by volume load. Cardiac output significantly increased during a volume load of 10 mL/kg at 1.7% enflurane but did not increase at 3.4% enflurane. Thus, the decrease in CO produced by 1.7% enflurane was reversed by increasing preload, but that produced by 3.4% enflurane was not reversed by increasing preload.

The HR was increased by about 30% using atrial pacing. The extent was approximately the same as that produced by $3-6 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ of dobutamine. Figure 4 shows percent changes in CO, E_{max} , MAP, HR, and LVEDP from control values (0% enflurane) in response to atrial pacing at 1.7% and 3.4% enflurane.

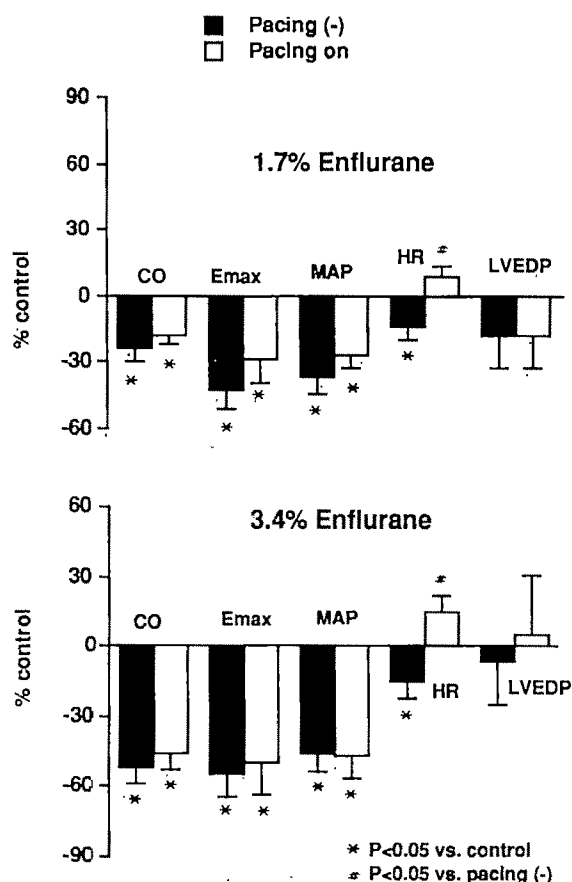


Figure 4. Effects of changes in the heart rate on hemodynamics during 1.7% and 3.4% enflurane. % Control, percent changes from control (0% enflurane); CO, cardiac output; E_{\max} , slope of end-systolic pressure-volume relationship; MAP, mean arterial pressure; HR, heart rate; LVEDP, left ventricular end-diastolic pressure.

rane. E_{\max} , MAP, and LVEDP remained unchanged during atrial pacing. Increasing HR did not significantly increase CO at 1.7% and 3.4% enflurane. Thus, the decreases in CO produced by 1.7% and 3.4% enflurane were not reversed by increasing the HR.

Discussion

The major findings in this study are that enflurane produced a dose-related depression of E_{\max} , indicating a decrease in cardiac contractility, and that a low dose of dobutamine was effective in reversing the depressed E_{\max} and hence CO. These findings suggest that increasing cardiac contractility is an effective approach if the hemodynamic depressant action of enflurane is to be countered.

Depression of myocardial contractile state by enflurane has been demonstrated both in vivo and in vitro in animals (1,5-7) as well as in humans (3). In isolated papillary muscle, enflurane decreases peak

developed tension, maximal rate of pressure development (dP/dt), tension-time interval, and time-to-peak tension (6,7). In isolated working hearts in vitro, enflurane shifted the left ventricular function curve down and to the right, indicating a depressed cardiac performance (5). In the intact animal heart in vivo, enflurane decreased CO, stroke volume, left ventricular stroke work, and left ventricular dP/dt (1,5). In humans, enflurane decreased CO, stroke volume, and aortic dP/dt (3). These studies leave little doubt that enflurane depresses the myocardial contractile state. However, these indices used in the in vivo heart are also influenced by changes in preload and/or afterload, which may be altered by anesthetics; i.e., the left ventricular dP/dt is directly related to the inotropism but is inversely related to the afterload (10,11). Therefore, a load-insensitive index is necessary when we examine the anesthetic-induced alterations of the inotropic state in the in situ heart.

The left ventricular end-systolic pressure-volume relationship is approximately linear over the working range of the heart, and the slope of the relation line (E_{\max}) is considered as a load-independent index of the inotropic state (12-15). We, therefore, used E_{\max} for assessment of contractility in this study. Igarashi and Suga (17) established a new method of assessing E_{\max} of the in situ heart, and this method has been adopted by other investigators to evaluate cardiac contractility (18,19). Although this method involves a few minor problems such as overlooking of the coronary flow during aortic occlusion and assuming the same contractile state between the paired ejection and isovolumic contraction phases, the observed E_{\max} was found to reflect the acute changes in the contractile state and to be unchanged despite the change in HR (16). In this study, E_{\max} increased during dobutamine infusion and remained unchanged by increasing HR with atrial pacing and volume load, suggesting that E_{\max} is useful as an index of contractility in the in situ dog heart. E_{\max} was decreased by 31% and 57% during 1.7% and 3.4% enflurane administration, respectively. This extent of depression of cardiac contractility is similar to that reported by others in guinea pigs (20) and in dogs (21).

The mechanisms by which volatile anesthetics depress myocardial contractility include depression of slow-channel-mediated Ca^{2+} entry and alteration of Ca^{2+} uptake and release by the sarcoplasmic reticulum, resulting in a reduction of the Ca^{2+} available to the contractile elements (21,22). Reduced sympathetic nervous system activity is another likely cause of cardiac depression during anesthesia (5). The fact that dobutamine can reverse the enflurane-induced depression of cardiac contractility may suggest that stimulation of the β -receptor-mediated Ca^{2+} channel

can overcome the reduction in the Ca^{2+} availability produced either directly or indirectly by enflurane.

We used enflurane to examine the depressant effect of volatile anesthetics on myocardial contractility and to delineate the effectiveness of increasing contractility during volatile anesthetic-induced circulatory depression, as enflurane has a depressant effect on the myocardium that is greater than that of isoflurane and similar to that of halothane (2,6,7,20,23). The differences among the inhaled anesthetics were mostly quantitative rather than qualitative in nature (23). The results of this study indicate that circulatory depression during halothane or isoflurane anesthesia may be counteracted by increasing myocardial contractility.

The aim of this study was to examine CO responses to therapeutic means during enflurane anesthesia, because the adjustment of CO is the principal objective of management of the circulatory system. We examined the CO responses to selective augmentation of preload, cardiac contractility, and HR. Increasing the preload (volume load 10 mL/kg) counteracted the decreased CO during 1.7% enflurane, but it was not effective during 3.4% enflurane. Increasing the HR was not effective at either 1.7% or 3.4% enflurane. Whereas increasing contractility was effective for the reversal of the enflurane-induced reduction of CO at both 1.7% and 3.4% enflurane, a low dose ($3 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) of dobutamine was enough to counteract the reduced CO by increasing cardiac contractility. The further increase in cardiac contractility by higher doses of dobutamine could not substantially increase CO (Figure 2). Sunagawa et al. (24) demonstrated the role of changes in preload, afterload, HR, and contractility in determining CO by using a mathematical analysis. They suggest that CO is determined predominantly by extracardiac factors, such as preload and afterload rather than cardiac contractility when the cardiac contractility is in the normal and supernormal range, and that cardiac contractility plays a significant role only when cardiac function is markedly deteriorated. Moreover, they demonstrated that HR was a less sensitive determinant of CO than cardiac contractility in such a condition. The results of our study are consistent with the above findings, showing a stronger relation of CO to the cardiac contractility as compared with the preload and HR during enflurane-induced cardiac depression. Therefore, increasing cardiac contractility seems to be a more logical therapeutic measure for the management of enflurane-induced circulatory depression.

Dobutamine was used to increase cardiac contractility, as it has a potent positive inotropic action with a relatively slight effect on preload, afterload, or HR (25,26). In this study, however, a dose-dependent

increase in the HR was observed, but it seems unlikely that the increase in HR could play a significant role in increasing CO as the increase in HR produced by atrial pacing to the same extent did not increase CO. The results of this study suggest the potential usefulness of other inotropic agents such as dopamine and ephedrine.

In summary, the results of our study demonstrate that increasing cardiac contractility by administration of a low dose of dobutamine can be a useful technique if hemodynamic depression during enflurane anesthesia is undesirable. However, increasing the preload and HR is not so effective in this situation. If the results of this experiment in dogs can be extrapolated to humans, then it is expected that circulatory depression during enflurane anesthesia is reversible with the use of inotropic drugs such as dobutamine.

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Acute Hypotension Caused by Rapid Hypertonic Saline Infusion in Anesthetized Dogs

Nguyen D. Kien, PhD, George C. Kramer, PhD, and David A. White, MD

Departments of Anesthesiology and Human Physiology, University of California, School of Medicine, Davis, California

Small volumes (4–6 mL/kg) of 7.5% hypertonic saline solution (HTS) are reported to be effective for resuscitation from circulatory shock. When infused rapidly into either hypovolemic or normovolemic subjects, HTS can cause an immediate and severe hypotension before cardiovascular improvement. In the present study, we examined the hypothesis that the early hypotension produced by HTS was mediated by an acute and transient depression of cardiac contractility. Left ventricular pressure and wall motions were measured simultaneously in 10 anesthetized dogs for the assessment of cardiac contractility. Infusion of HTS at 3 mL/kg in 1 min significantly decreased mean arterial blood pressure by 49%, from 95 ± 4 to 51 ± 5 mm Hg ($P < 0.05$, mean \pm SEM) at 45 s after the onset of infusion. This initial decrease in arterial blood pressure was abrupt and transient (106 ± 9 s). Concomitantly, cardiac output and coronary blood flow increased significantly from 2.8 ± 1.0 to $3.9 \pm$

1.1 L/min and from 23.7 ± 5.3 to 49.8 ± 4.7 mL/min, respectively. Although heart rate remained constant, systolic shortenings of left ventricular diameter and wall thickness increased from $5.6\% \pm 0.5\%$ to $7.8\% \pm 0.5\%$ and from $13.9\% \pm 0.6\%$ to $15.1\% \pm 1.2\%$, respectively, indicating an improvement in cardiac contractility. This was confirmed by subsequent analysis of the left ventricular end-systolic pressure-diameter relationship. Systemic and pulmonary vascular resistance decreased by 60% and 27%, respectively. Despite an initial period of hypotension after rapid infusion of HTS, mean arterial blood pressure, cardiac output, and contractility were all significantly increased at 5 min after HTS infusion. The results show that acute hypotension caused by rapid infusion of HTS was not mediated by cardiac depression but by a decrease in total peripheral resistance.

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In 1980, Velasco et al. reported that dogs subjected to severe hemorrhagic shock were successfully resuscitated with a small bolus infusion of 7.5% hypertonic saline solution (HTS) (1). The beneficial effects of HTS have been subsequently verified in various studies of hemorrhage and resuscitation in sheep (2,3), rats (4,5), and dogs (6). The results of these studies demonstrate that HTS infusion in small volumes, 4–6 mL/kg, rapidly improves cardiovascular and metabolic function by a combination of plasma volume expansion, peripheral vasodilation, and augmented myocardial performance.

For each milliliter of HTS infused, plasma volume rapidly increases by 2–4 mL because of a fluid shift into the vascular compartment secondary to increases in intravascular osmotic pressure (3,7,8). Whereas the plasma volume expansion is related to the increased

sodium concentration, a profound vasodilation is reported to accompany increases in osmolality (9). This HTS-induced vasodilation is of particular importance as it decreases the increased vascular resistances associated with circulatory shock and facilitates maintaining a normal cardiac output and its distribution (10–12). In addition to increased venous return and reduced afterload, the improvement in cardiac output is attributed to a positive inotropic effect of HTS (13,14). It appears that resuscitation from hemorrhagic shock with HTS provides rapid restoration of circulatory function that allows compensation for oxygen debt induced by hemorrhage (15) and improves survival by limiting the tissue damage caused by ischemic injury (1,16–19).

In addition to the potential benefit for the treatment of hemorrhagic shock, hypertonic solutions are effective in the management of hypovolemia associated with major operative procedures (20,21), suggesting a potential use of these solutions in intraoperative or postsurgical resuscitation.

Nevertheless, an immediate and severe systemic hypotension before cardiovascular improvement has

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Address correspondence to Dr. Kien, Department of Anesthesiology, TB-170, School of Medicine, University of California, Davis, CA 95616.

been observed in our laboratory after rapid infusion ($>1.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) of HTS in anesthetized dogs. It has been hypothesized that this initial hypotension is mediated by a decrease in cardiac output owing to an acute depression of cardiac contractility (22). Because the systemic hypotension associated with rapid infusion of HTS could be particularly detrimental in the presence of severe hemorrhage or cardiovascular or cerebral vascular disease, the present study was motivated by our concerns over the safety of rapid infusions of HTS. It was designed to evaluate the immediate cardiovascular effects of HTS.

Methods

Experiments were conducted in 10 mongrel dogs of either sex weighing 19–25 kg. Anesthesia was induced by thiamylal (15 mg/kg). After tracheal intubation, anesthesia was maintained with 1.5% halothane in oxygen. Ventilation was controlled to maintain arterial CO_2 tension at 35–40 mm Hg. Systemic arterial pressure was transduced from a fluid-filled catheter inserted through a femoral artery into the abdominal aorta. Pulmonary arterial and central venous pressures were measured from a balloon-tipped catheter placed in the pulmonary artery. Through a thoracotomy at the fifth intercostal space, a miniature pressure transducer (Königsberg, P7, Pasadena, Calif.) was implanted into the left ventricle (LV) through a stab wound in the apex to measure left ventricular pressure. The Königsberg transducer was calibrated *in vitro* against a mercury manometer and *in vivo* against aortic systolic and left atrial pressures. Frequent calibration was made to compensate for electrical drift. Body temperature was maintained at $37 \pm 1^\circ\text{C}$ with a heating pad.

Left ventricular end-diastolic pressure and the rate of change of pressure (dP/dt) were derived from the left ventricular pressure tracing. Pulse-transit time ultrasonic dimension transducers were implanted in pairs to measure the anterior-posterior minor axis diameter and the endocardium-epicardium wall thickness of the left ventricle. These transducers operate on the principle of measuring the transit time of ultrasonic impulses between piezoelectric crystals. Proper alignment of the paired transducers was confirmed with a high-frequency oscilloscope (Textronix, RM 674, Beaverton, Ore.). Left ventricular dimensions were monitored with a sonomicrometer (Triton, 120, San Diego, Calif.). Hydraulic occluders were placed around both vena cavae for varying preload during assessment of LV contractility. Cardiac output and coronary blood flow were measured from flow probes placed around the ascending aorta and left anterior descending coronary artery using either electromagnetic or ultrasonic flowmetry (Zepeda, SWF-5RD, Seattle, Wash. or Transonic, T101,

Ithaca, N.Y.). Data were recorded on a direct-writing recorder and on magnetic tape for later analysis. Signals from the dimension transducers, LVP, LV dP/dt , and arterial blood pressure were channeled into a 80386 microprocessor, digitized at 5-ms intervals by a Techmar 12-bit analog-to-digital converter, and stored on floppy disks for analysis.

After completion of the surgical preparation, the end-tidal halothane concentration was reduced to 1.0%, measured by mass spectrometry. Experiments were conducted after stability of cardiovascular function and normal arterial blood gas tensions were observed for 30 min. Hypertonic saline solution (3 mL/kg) was infused intravenously for 1 min. Data were recorded continuously before and during the 15 min after HTS infusion. At the end of the experiment, the dog was killed with a halothane overdose and an intravenous injection of saturated KCl.

Data were analyzed using an Asyst program (Asyst, Rochester, N.Y.). Variables, including mean arterial blood pressure, stroke volume, systemic vascular resistance, and pulmonary vascular resistance were calculated using standard formulas. Cardiac contractility was assessed using percent of systolic shortening (dimension change during systole divided by end-diastolic dimension) to reflect regional performance and to provide continuous assessment of contractility. Cardiac performance was evaluated using the linear regression slope of the LV end-systolic pressure-diameter relationship. Ten to 15 consecutive heart beats during vena caval occlusion were analyzed at end-systole. To eliminate any respiratory influence on hemodynamic measurements, cardiac contractility was assessed while the respirator was momentarily turned off. The autonomic sympathetic reflex caused by vena caval occlusion was minimized by eliminating heart beats with RR intervals varying more than 10% from the preocclusion level. Analysis of the cardiac cycle was performed by computer gating. For each heart beat, end-systole was defined as 20 ms before the peak negative LV dP/dt and end-diastole was assumed at the beginning of the rapid rise in left ventricular pressure. The slope, E_{es} , of the end-systolic pressure-diameter relationship was calculated using the equation: $P_{\text{es}} = E_{\text{es}}(D_{\text{es}} - D_d)$, where P_{es} and D_{es} are LV end-systolic pressure and diameter, respectively, and D_d is the intercept of the diameter axis. This slope has been found independent of loading conditions and closely related to the inotropic state of the heart (23,24).

Data were expressed as mean \pm SEM. Statistical analysis included analysis of variance for repeated measures and paired *t*-test with Bonferroni correction. Difference was considered significant at probability less than 0.05. This study was approved by our

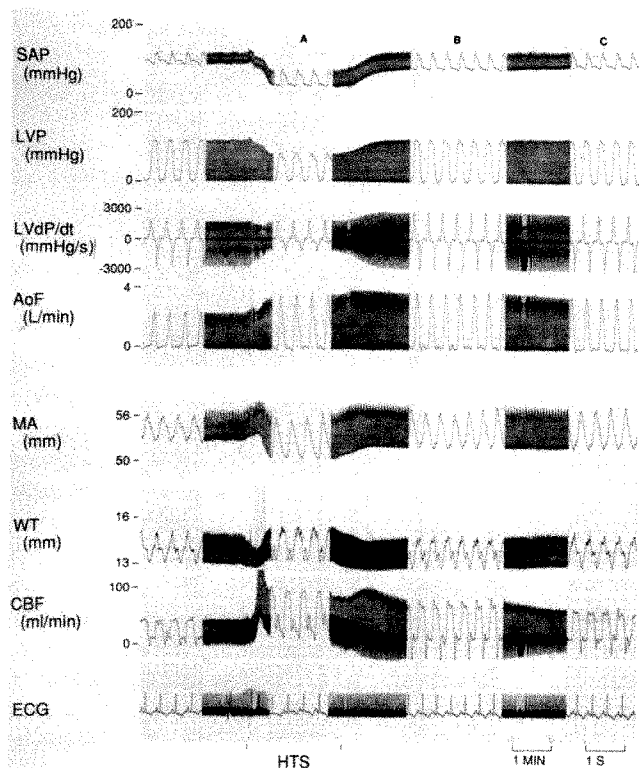


Figure 1. An original recording from one dog showing cardiovascular responses to HTS. From top to bottom are displayed systemic arterial pressure (SAP), left ventricular pressure (LVP), the first derivative of LVP (LV dP/dt), aortic flow (AoF), minor axis diameter of the LV (MA), wall thickness of the LV (WT), coronary blood flow (CBF), and electrocardiogram (ECG). Intravenous infusion of 3 mL/kg of HTS for 1 min causes biphasic responses characterized by acute decreases and followed by more sustained increases in SAP, LVP, and LV dP/dt. Aortic and coronary blood flows increase abruptly and remain elevated throughout the first 5 min. Recordings were made at slow speed (2 cm/min) and fast speed (2 cm/s) at 45 s (A), 2.5 min (B), and 5 min (C) after onset of infusion.

institutional committee on the care and use of laboratory animals.

Results

A 1-min infusion of 3 mL/kg of HTS produced a biphasic response in arterial blood pressure (Figure 1). An initial decrease in MAP, reaching its peak before the completion of infusion, was abrupt and transient (106 ± 19 s). This phase of acute hypotension was followed by a gradual increase in arterial blood pressure, which reached its plateau by 5 min. The results shown in Table 1 represent peak hemodynamic responses, which occurred at 45 s and at 5 min after the onset of HTS infusion. Thus, we compare these variables for their immediate response during infusion with their response 5 min after the onset of the infusion.

Mean arterial pressure decreased 49% (from 95 ± 4

Table 1. Systemic Responses to Rapid Hypertonic Saline Infusion

	Baseline	Time after HTS administration	
		45 s	5 min
HR (beats/min)	101 ± 8	103 ± 6	114 ± 9^a
MAP (mm Hg)	95 ± 4	51 ± 5^a	$113 \pm 8^{a,b}$
PP (mm Hg)	35 ± 3	48 ± 4^a	47 ± 4^a
MPAP (mm Hg)	14 ± 1	17 ± 1^a	15 ± 1
CO (L/min)	2.3 ± 1.0	3.9 ± 1.1^a	4.0 ± 0.9^a
SV (mL)	26.4 ± 1.5	38.5 ± 1.9^a	34.3 ± 2.1^a
SVR (dynes·s·cm ⁻⁵)	2623 ± 220	1069 ± 159^a	$2071 \pm 367^{a,b}$
PVR (dynes·s·cm ⁻⁵)	261 ± 18	187 ± 16^a	174 ± 23^a

HTS, hypertonic saline solution; HR, heart rate; MAP, mean arterial blood pressure; PP, pulse pressure; MPAP, mean pulmonary arterial pressure; CO, cardiac output; SV, stroke volume; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Values represent the mean \pm SEM of 10 dogs.

^a $P < 0.05$ compared with baseline.

^b $P < 0.05$ compared with 45 s.

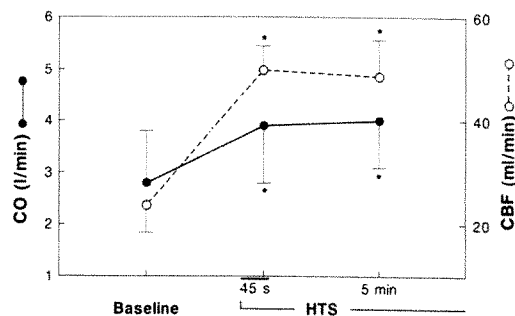


Figure 2. Effects of rapid infusion of hypertonic saline solution (HTS) on cardiac output (CO) and coronary blood flow (CBF). Significant increases in both CO and CBF are observed at 45 s and 5 min after the onset of infusion. The infusion of HTS causes vasodilation in both peripheral and coronary vascular beds. Values are mean \pm SEM of 10 dogs. * $P < 0.05$ compared with baseline.

to 51 ± 5 mm Hg) at 45 s, and increased significantly above baseline at 5 min. Left ventricular end-diastolic pressure increased and remained above baseline after HTS. This increase in left ventricular end-diastolic pressure after HTS suggests that the initial hypotension was not due to a reduction in preload. The vasodilator effect of HTS was signified by a decrease in vascular resistance and by an immediate increase in pulse pressure. Similar increases in cardiac output and coronary blood flow were observed throughout the first 5 min of HTS infusion (Figure 2). Heart rate did not change initially but increased significantly above baseline at 5 min. Stroke volume increased 35% during peak hypotension; this increase was sustained despite the tachycardia that developed during the recovery of arterial pressure.

Systolic shortenings of both minor axis diameter and wall thickness of the LV increased simultaneously during infusion. Systolic shortening re-

Table 2. Cardiac Responses to Rapid Hypertonic Saline Infusion

	Baseline	Time after HTS administration	
		45 s	5 min
LVP (mm Hg)	118 ± 3	68 ± 7 ^a	124 ± 9 ^{a,b}
LVEDP (mm Hg)	4 ± 1	9 ± 1 ^a	8 ± 1.0 ^a
LV dP/dt (mm Hg/s)	1890 ± 124	1465 ± 102 ^a	2103 ± 197 ^b
CBF (mL/min)	23.7 ± 5.3	49.8 ± 4.7 ^a	48.6 ± 7.1 ^a
E _{es} (mm Hg/mm)	12.4 ± 2.6	—	15.8 ± 2.9 ^a
% SS of MA	5.6 ± 0.5	7.8 ± 0.5 ^a	7.5 ± 0.7 ^a
% SS of WT	13.9 ± 0.6	15.1 ± 1.2	16.2 ± 1.0 ^a

HTS, hypertonic saline solution; LVP, left ventricular pressure; LVEDP, left ventricular end-diastolic pressure; LV dP/dt, rate of change of LVP; CBF, coronary blood flow; E_{es}, slope of the LV pressure-diameter relationship; % SS, percent of systolic shortening; MA, minor axis diameter of LV; WT, wall thickness.

Values represent the mean ± SEM of 10 dogs.

^a*P* < 0.05 compared with baseline.

^b*P* < 0.05 compared with 45 s.

maintained increased at 5 min. Table 2 shows a significant increase in E_{es} measured at 5 min after HTS as compared with baseline. Because vena caval occlusion was necessary during the assessment of contractility (using E_{es} as an index), the measurement of E_{es} was not possible at 45 s owing to the interference of vena caval occlusion with the continuous monitoring of other physiologic variables. Changes in LV dP/dt were closely related to those of arterial blood pressure, reflecting the load-dependent characteristic of this index of contractility. Systemic and pulmonary vascular resistances decreased by 60% and 27%, respectively, at 45 s. Whereas the decrease in pulmonary vascular resistance persisted, systemic vascular resistance increased above the 45-s level; but it remained significantly lower than baseline at 5 min.

Discussion

The clinical benefits of HTSs in the treatment of hyponatremia, Buerger's disease, and burn injury have been well described (25-27). Recently, the clinical application of 7.5% HTS has extended to the treatment of hemorrhagic shock and has showed encouraging results. De Fellipe et al. (28) reported that HTS promptly reversed shock in patients with refractory hypovolemia. In patients undergoing vascular surgery, HTS was found safe and effective for perioperative treatment of extracellular fluid deficit (20,21). With the addition of 6% dextran 70 to sustain the improvement in cardiovascular function, resuscitation using small volumes of HTS resulted in a better survival rate than using lactated Ringer's solution in severely injured patients (29). The results of these studies indicate that HTS is a promising solution for resuscitation of hypovolemia.

The present study demonstrates a brief but severe hypotension associated with rapid infusion of HTS. The hypothesis that hypotension is due to a decrease in cardiac output and/or a depression in myocardial function is rejected based on the data of this study. Conversely, we found that cardiac contractility was well maintained and was accompanied by increases in cardiac output and coronary perfusion that were sustained beyond the initial decrease in arterial blood pressure.

Hypertonic saline solution as administered in this study clearly had no depressant effects on myocardial contractility. Although the measurement of E_{es} was not possible during the peak hypotension immediately after rapid infusion of HTS, the increases in stroke volume, coronary blood flow, and myocardial systolic shortenings indicated that the initial decrease in arterial blood pressure was not concurrent to a depression in myocardial function. On the contrary, increases in serum osmolality associated with administration of hypertonic solutions of saline, glucose, urea, or mannitol were reported to improve cardiac contractility in various studies. Hyperosmolality increased V_{max} and the isometric tension developed by isolated papillary muscle (30,31). In intact dogs with controlled heart rate, aortic pressure, and cardiac output, moderate increases in osmolar concentration were associated with augmented contractile forces of the LV (13). Previously, we reported a positive inotropic effect of HTS after either intravenous or intraarterial infusion into normotensive dogs (14). Similar cardiac improvements have been observed after HTS resuscitation from either hemorrhagic (32,33) or septic shock (34).

Although the mechanism by which HTS increases cardiac inotropy remains unclear, the cardiac effects of HTS have been found independent of the autonomic system and peripheral osmoreceptors (13,14). Increases in osmolality have been demonstrated to alter mechanical characteristics of both contractile and series elastic elements of cardiac muscle (31). It is postulated that activity of the contractile elements could be facilitated when intracellular water concentration is decreased by hyperosmolality (30). Additionally, the increased contractile performance of cardiac muscle has been found closely associated with changes in osmolal level (13). Moderate elevations of osmolality, similar to those induced by clinical doses of HTS, enhanced myocardial contractility by an increase in intracellular calcium concentration secondary to dehydration of cardiac myocytes. However, when osmolality exceeded the normal level by 100 mOsm/L, a depression in contractile function was observed probably owing to the developed friction between contractile elements of severely dehydrated fibers (13,30,31). This cardiac depressive effect of

extreme hyperosmolality may provide an explanation for the reported negative inotropic response to HTSs infused directly into the heart (32,35,36).

The use of the left ventricular end-systolic pressure-diameter relationship for assessing cardiac contractility is controversial. This linear relationship becomes convex toward the volume axis when the ventricular volumes decrease below or exceed normal physiologic limits. Therefore, the E_{es} as an index of contractility may be unreliable over a wide range of ventricular volumes (37-39). In the present study, paired data of left ventricular end-systolic pressure and diameter during 10-15 heart beats were used for each regression analysis. The first heart beat in the series for analysis was selected at the onset of blood pressure reduction so that the changes of pressure and diameter during vena caval occlusion were within physiologic ranges. When determined over these limited ranges, E_{es} remained to be a relatively accurate index of the inotropic state (38).

One of the major findings of this study is that HTS induces immediate and remarkable increases in aortic and coronary blood flows (Figure 2). A combination of expanded plasma volume, peripheral vasodilation, and augmented myocardial contraction is believed to contribute to the increase in cardiac output. It is clear that HTS exerts potent vasodilator effects on both peripheral and coronary vessels. The reduction in peripheral vascular resistance observed in the present study is consistent with those reported in previous studies after similar increases in plasma osmolality (2-4,14-17,32,33). It is important to note that locally mediated vasodilation associated with hyperosmolality can occur with salt-free hypertonic solutions, suggesting that vasodilation is not dependent on the increased sodium ion (9). Instead, the active vasomotion of the smooth muscle cells caused by osmotic changes may be responsible for the decrease in vascular resistance (40). Whether the osmotic changes also trigger a release of vasoactive substances from blood or tissue that mediates the active vasomotion is not known and merits further investigation.

Rapid infusion of HTS caused an initial decrease in arterial blood pressure consistent with peripheral vasodilation. Similar hypotensive responses have been reported in previous investigations; however, its mechanism remains controversial (41-43). Holland et al. (41) postulated that the decrease in arterial blood pressure after rapid intracarotid injection of hypertonic solutions was due to direct inhibition of medullary vasomotor centers. This is at variance with findings reported by Read et al. (42) who concluded that the hypotensive response to hyperosmolality was independent of central nervous system activity and was related to peripheral osmolal effects. Based on the absence of hypertensive response to repeated

hyperosmolar challenges, Stiff et al. (43) suggested a mediator involvement responsible for the vasodilator effect of hyperosmolality.

Although HTS infusion at $2 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ is effective for resuscitation of moderate to severe hypovolemia in various studies without deleterious consequences (2-4,7,10), it would seem prudent to infuse HTS with caution and at a slower rate because hypotensive responses may be exaggerated in the presence of severe injuries or preexisting diseases. Efficient resuscitation using isotonic crystalloids requires that large volumes of fluid be administered rapidly for early restoration of hemodynamics (44). Aggressive fluid resuscitation therapy, including multiple venous cannulations, placement of large-bore catheters, and use of pressurized fluid delivery systems, is often used in the prehospital setting and in emergency rooms. However, whether HTS can be safely infused at rates equal to those used with isotonic crystalloid resuscitation is unknown as the cardiovascular effects of rapid HTS infusion have not been fully examined.

In summary, rapid infusion of HTS in anesthetized dogs is associated with an acute hypotension secondary to a decrease in systemic vascular resistance. Increases in cardiac output, coronary blood flow, and ventricular contractility simultaneous to the decrease in arterial blood pressure indicate that cardiac dysfunction is not the mechanism of the initial hypotension. Whereas a brief hypotension is well tolerated when circulatory function is normal, in the presence of severe hypovolemia, vascular disease, or compromised organ function, an acute decrease in perfusion pressure may exacerbate the underlying injury and lead to detrimental consequences. Although resuscitation from hemorrhagic shock is successful using small volumes of HTS, the present study suggests that HTS should be given slowly to avoid or to minimize an acute hypotensive response.

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Actions of Halothane, Isoflurane, and Enflurane on the Regional Action Potential Characteristics of Canine Purkinje Fibers

Stojan Polic, MD, PhD, Zeljko J. Bosnjak, PhD, Jure Marijic, MD, Raymond G. Hoffmann, PhD, John P. Kampine, MD, PhD, and Lawrence A. Turner, MD

Anesthesia Research Laboratory, Departments of Anesthesiology and Physiology, The Medical College of Wisconsin, Milwaukee, Wisconsin

The effects of halothane, isoflurane, and enflurane on proximal (false tendon) and distal (apical) canine Purkinje fibers were measured in vitro to assess their comparative effects on fibers exhibiting characteristically long (proximal) and short (distal) action potential duration. High- and low-dose anesthetic effects were evaluated in three groups of six left ventricular preparations and were compared with the changes occurring at identical times in six control preparations using analysis of variance with repeated measures. Under control conditions in all groups, the action potential duration, measured at 90% repolarization (APD_{90} , mean \pm SEM), of proximal fibers was longer than that of distal fibers (320 ± 16 vs 252 ± 11 ms, $P \leq 0.01$). Halothane (0.3 and 0.7 mM), isoflurane (0.4 and 0.8 mM), and enflurane (0.6 and 1.0 mM)

produced a dose-dependent decrease ($P \leq 0.01$) of proximal fiber APD_{90} with less ($P \leq 0.01$) change of distal fiber APD_{90} and reduced ($P \leq 0.05$) regional differences of APD_{90} at the higher dose. The decreases of proximal fiber APD_{90} were greater ($P \leq 0.01$) for 1.0 mM (1.7 MAC) enflurane (-66 ± 7 ms) and 0.8 mM (3.0 MAC) isoflurane (-69 ± 9 ms) than for 0.7 mM (2.9 MAC) halothane (-33 ± 8 ms). We conclude that the regional actions of anesthetics on Purkinje fiber repolarization may influence conduction during the relative refractory period and the occurrence of arrhythmias associated with disparity of regional refractory characteristics in the ventricular conduction system.

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The electrophysiologic actions of the volatile anesthetics on cardiac tissues are of interest because they may influence the occurrence or severity of perioperative arrhythmias. Although halothane, isoflurane, and enflurane are widely used anesthetics, little is known about their comparative effects on the action potential and refractory characteristics of Purkinje fibers within the specialized ventricular conduction system.

The actions of halothane on the transmembrane potentials of cardiac Purkinje fibers include marked changes in the action potential contour characterized by increased slope of the plateau phase (1). Haus-

wirth (2) compared the effects of halothane on the repolarization phase of sheep ventricular muscle and of Purkinje fibers at constant paced rate. The effects of halothane on the action potentials of Purkinje fibers were more prominent than those on muscle fibers and included slight hyperpolarization of the maximum diastolic potential and reduction of the overshoot, the rate of phase 0 depolarization (\dot{V}_{max}), and the conduction velocity, as well as marked shortening of the action potential duration (APD) and effective refractory period. Gallagher et al. (3) reported that halothane decreased canine Purkinje fiber APD measured at 50% repolarization (APD_{50}), whereas it increased APD measured at 100% repolarization (APD_{100}). On the other hand, observations from our laboratory (4) indicate that halothane reduces the APD_{90} of canine Purkinje fibers derived from regions of the conduction system exhibiting characteristically prolonged APD_{90} (false tendon fibers) without reducing APD_{90} of fibers isolated from regions exhibiting shorter APD_{90} (apical fibers) in a manner comparable to the actions of lidocaine (5) and

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Address correspondence to Dr. Turner, Department of Anesthesiology, The Medical College of Wisconsin, MFRC/A1000, 8701 West Watertown Plank Road, Milwaukee, WI 53226.

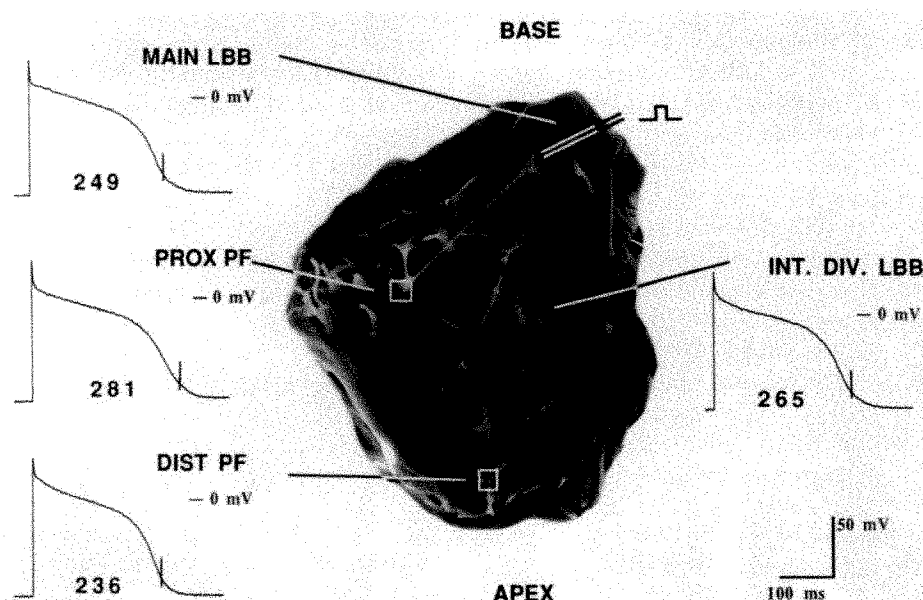



Figure 1. Action potential duration (APD₉₀, in ms) of Purkinje fibers in several regions of a control preparation stimulated at 75 beats/min. LBB, left bundle branch; PROX and DIST PF, proximal and distal Purkinje fibers. , Site of bipolar extracellular stimulation.

the Na⁺ channel antagonist tetrodotoxin (6). The actions of halothane abbreviating repolarization of Purkinje fibers in vitro are consistent with its actions shortening refractory periods in the ventricular conduction system in vivo (7). The possibility that isoflurane and enflurane may also produce differential regional effects on Purkinje fiber action potential characteristics has not been reported. Therefore, we sought to evaluate the comparative dose-related effects of halothane, isoflurane, and enflurane on the action potentials of Purkinje fibers derived from two specific regions of the canine left ventricular conduction system exhibiting characteristically long and short APD.

Methods

The protocol for this study was reviewed and approved by the Animal Care Committee of the Medical College of Wisconsin. Twenty-four unconditioned adult mongrel dogs weighing 12–22 kg were anesthetized with halothane in oxygen and were killed by rapid excision of the heart. After isolation, the hearts were rinsed and dissected in cold oxygenated Tyrode's solution of the following composition (mM): NaCl 137, KCl 4.0, CaCl₂ 1.8, MgCl₂ 0.5, NaH₂PO₄ 1.8, NaHCO₃ 16, and dextrose 5.5. The atria and right ventricle were removed, and the left ventricle was rapidly dissected to yield a 4- by 5-cm preparation (4) that was mounted endocardial surface upward in a 50-mL tissue chamber. The preparations were superfused at 25 mL/min with 37°C Tyrode's solution

equilibrated with a 97% O₂/3% CO₂ mixture (pH 7.30–7.35). Each preparation (Figure 1) consisted of the left anterior papillary muscle and portions of the apex, paraseptal free wall, and base of the interventricular septum and included the anterior false tendon from its origin at the septal portion of the main left bundle branch to its junction with the papillary muscle.

After 90 min of equilibration, action potentials were recorded from the most superficial Purkinje fiber encountered on advancing a glass microelectrode (resistance, 10–30 Mohms) toward the endocardial surface. The preparations were stimulated at a constant rate of 75 beats/min using bipolar electrodes placed on the endocardial surface of the left bundle branch (LBB) at the false tendon origin. The drive stimuli were rectangular pulses of 1.5× threshold intensity derived from a programmable digital stimulator (4). The action potential signals were amplified, sampled, stored in computer memory (HP 9000/S330, Hewlett Packard Co., Fort Collins, Colo.) and the maximum rate of phase 0 depolarization (\dot{V}_{max}) was measured in volts per second by electronic differentiation as described previously (6). The data were processed to obtain the following action potential characteristics: in millivolts, the maximum diastolic potential, overshoot, and amplitude; and in milliseconds, the action potential duration measured at 50%, 70%, 90%, and 95% of complete repolarization (APD₅₀, APD₇₀, APD₉₀, APD₉₅). Regional action potential characteristics were evaluated by recording from 10 consecutively impaled fibers located at each

of two discrete (1×2 mm) sites in each preparation under each experimental condition. One site (Figure 1) was located at the false tendon–anterior papillary muscle junction (proximal fibers), and a second site (distal fibers) was located 2–3 cm toward the cardiac apex from the proximal recording site. Purkinje fibers from these regions are well known to exhibit characteristically long (proximal) and short (distal) APDs (8). The action potential data from 10 proximal and 10 distal fibers were pooled by region to develop average values of the measured characteristics at each site under each experimental condition over a period of approximately 30 min.

The action potential responses to halothane, isoflurane, and enflurane were determined in three groups of six hearts studied in the following sequence: control 1, high dose; control 3, low dose, and control 5 in experiments lasting 6–7 h. The influence of time on the action potentials was also evaluated in a control group of six hearts studied in an analogous manner at identical times (control 1 to control 5) and referred to as the no-anesthetic group. In the anesthetic groups, the washin period for each dose was 20 min (approximately 10 time constants), and the washout period was 60 min. These time periods were selected on the basis of preliminary studies demonstrating that they were sufficient to result in no further changes in the repolarization characteristics of single continuously impaled fibers with additional exposure to each agent. The anesthetics were introduced by switching to a reservoir of solution pre-equilibrated at room temperature with the agents by passing the O_2/CO_2 mixture through calibrated vaporizers. The vaporizers were initially set to high concentrations and allowed to equilibrate for 1.5 h. The low dose of each agent was prepared by 1:1 dilution of the high-dose solution and by equilibration at one-half the initial vaporizer setting. The anesthetic concentrations in the tissue chamber at equilibrium, determined by gas chromatography, were as follows: halothane, 0.74 ± 0.16 mM (2.5 vol%) and 0.31 ± 0.04 mM (1.1 vol%); isoflurane, 0.82 ± 0.08 mM (3.8 vol%) and 0.41 ± 0.02 mM (1.9 vol%); and enflurane, 1.00 ± 0.09 mM (3.5 vol%) and 0.57 ± 0.07 mM (2.0 vol%) at the high and low doses, respectively. The dose levels obtained, in terms of volume percent and MAC multiples of each anesthetic (9), were calculated (10) from the mean values of the millimolar bath concentrations using the liquid/gas partition coefficient of a similar Krebs' solution (11).

The action potential characteristics obtained were evaluated by analysis of variance for three factors (group, site, time or dose) with repeated measures (time, site) and are presented in terms of mean \pm SEM. The within- and between-group means and mean changes from preceding control were compared by the

Waller-Duncan LSD (least significant difference) method (12) based on the variance of all 24 preparations for each measured characteristic. A probability level of 0.05 or less was considered significant.

Results

The action potentials of fibers located in several regions of the canine left ventricular conduction system are shown in Figure 1. In this control preparation, the APD_{90} of fibers located at the false tendon–anterior papillary muscle junction (designated as proximal fibers) was longer than that of fibers overlying the apical endocardium (designated as distal fibers) or fibers located within either the main LBB near its origin or the internal division of the LBB overlying the septum. To assess the anesthetic effects on Purkinje fibers exhibiting long and short APD, the responses of proximal and distal fibers were measured in an identical manner under each condition. The mean values of each action potential characteristic in the anesthetic groups are given in Table 1.

Membrane Potentials and Upstroke Characteristics

The maximum diastolic potential differed slightly between groups (mean values ranging from 84.1 ± 0.4 mV in the enflurane group to 86.4 ± 0.6 mV in the no-anesthetic group, $P \leq 0.05$, averaged by region and time) and between regions (86.1 ± 0.4 mV for proximal fibers vs 84.0 ± 0.3 mV for distal fibers, $P \leq 0.05$, averaged by group and time), but did not exhibit significant time or anesthetic effects. Similarly, the overshoot differed between groups (values ranging from 32.9 ± 0.9 mV in the halothane group to 36.9 ± 0.5 mV in the no-anesthetic group, $P \leq 0.05$, averaged by region and time) and by region (33.4 ± 0.5 mV for proximal fibers vs 35.4 ± 0.5 mV for distal fibers, $P \leq 0.05$, averaged by group and time). In addition, the overshoot exhibited time-dependent decreases in several groups and moderate depression ($P \leq 0.05$) relative to the preceding control mean in the presence of 1.0 mM enflurane at both proximal and distal regions. The amplitude also differed between groups (values ranging from 118.1 ± 0.6 mV for the enflurane group to 123.1 ± 0.7 mV in the no-anesthetic group, $P \leq 0.05$, averaged by region and time) and decreased moderately over time but did not differ between the two regions. The amplitude of distal but not proximal fibers was reduced ($P \leq 0.05$) in the presence of 1.0 mM enflurane relative to preceding control. The rate of phase 0 depolarization (V_{max}) did not exhibit significant between-group differences or deterioration over time and only tended to show slightly greater mean values for proximal fibers (458 ± 20 V/s) than for distal fibers (411 ± 18 V/s).

Table 1. Effects of Halothane, Isoflurane, and Enflurane on the Action Potential Characteristics of Proximal and Distal Purkinje Fibers

	MDP (mV)	OS (mV)	Amp (mV)	\dot{V}_{max} (V/s)	APD ₅₀ (ms)	APD ₉₀ (ms)
Halothane						
Proximal PF						
Control 1	-86.5 ± 1.5	32.4 ± 1.4	118.9 ± 2.0	417 ± 26	246 ± 9	301 ± 10
0.7 mM HAL	-85.6 ± 0.7	32.1 ± 0.7	117.5 ± 1.6	451 ± 41	194 ± 7 ^a	268 ± 6 ^a
Control 3	-84.5 ± 1.5	31.2 ± 1.1	115.7 ± 2.2	455 ± 50	241 ± 6 ^b	305 ± 6
0.3 mM HAL	-85.2 ± 1.0	31.5 ± 1.2	114.9 ± 1.8	475 ± 55	231 ± 4 ^a	299 ± 6 ^a
Control 5	-84.9 ± 1.0	31.4 ± 0.8	116.2 ± 1.4	431 ± 36	251 ± 6 ^b	314 ± 6 ^b
Distal PF						
Control 1	-82.0 ± 1.3	35.9 ± 1.3	117.9 ± 2.0	444 ± 27	203 ± 8	255 ± 8
0.7 mM HAL	-83.6 ± 1.1	34.9 ± 1.5	118.5 ± 2.1	459 ± 68	191 ± 6 ^a	251 ± 6
Control 3	-82.9 ± 0.7	33.1 ± 1.4 ^b	116.0 ± 1.8	394 ± 25	213 ± 6 ^b	264 ± 6 ^b
0.3 mM HAL	-84.0 ± 0.8	34.0 ± 1.1	118.0 ± 1.5	365 ± 42	217 ± 5	273 ± 6 ^a
Control 5	-84.2 ± 0.8	32.1 ± 1.6 ^b	116.3 ± 1.5	353 ± 38	225 ± 7 ^b	274 ± 6 ^b
Isoflurane						
Proximal PF						
Control 1	-86.2 ± 0.4	33.8 ± 0.9	119.9 ± 0.8	423 ± 28	243 ± 7	303 ± 6
0.8 mM ISO	-86.4 ± 0.8	32.7 ± 1.0	119.4 ± 0.7	426 ± 21	151 ± 11 ^a	234 ± 8 ^a
Control 3	-87.2 ± 0.6	33.8 ± 0.9	120.9 ± 1.0	451 ± 22	235 ± 3 ^b	297 ± 4 ^b
0.4 mM ISO	-87.5 ± 0.5	33.4 ± 0.8	120.9 ± 0.7	456 ± 23	203 ± 5 ^a	275 ± 6 ^a
Control 5	-85.9 ± 0.6	31.9 ± 0.6 ^b	117.8 ± 1.0	397 ± 17	241 ± 3	307 ± 4
Distal PF						
Control 1	-85.7 ± 0.5	35.9 ± 1.0	121.5 ± 1.2	424 ± 20	181 ± 8	232 ± 9
0.8 mM ISO	-84.6 ± 0.6	34.8 ± 0.9	119.3 ± 0.7	400 ± 19	143 ± 10 ^a	207 ± 8 ^a
Control 3	-82.9 ± 1.0	34.6 ± 0.9	117.6 ± 1.1	364 ± 20	185 ± 7	239 ± 8 ^b
0.4 mM ISO	-84.3 ± 1.0	33.4 ± 1.2	117.7 ± 0.8	369 ± 25	185 ± 7	242 ± 6
Control 5	-82.9 ± 1.1	34.5 ± 1.0	117.4 ± 0.8 ^b	373 ± 23	203 ± 6 ^b	257 ± 4 ^b
Enflurane						
Proximal PF						
Control 1	-85.1 ± 1.0	33.4 ± 1.0	118.5 ± 1.3	408 ± 40	253 ± 11	308 ± 10
1.0 mM ENF	-84.5 ± 1.2	31.2 ± 1.2 ^a	115.6 ± 2.1	424 ± 39	139 ± 12 ^a	242 ± 11 ^a
Control 3	-85.3 ± 0.9	32.2 ± 0.2	117.4 ± 0.8	468 ± 62	250 ± 11	316 ± 11 ^b
0.6 mM ENF	-84.6 ± 1.4	31.6 ± 1.2	116.2 ± 1.8	456 ± 72	193 ± 11 ^a	285 ± 11 ^a
Control 5	-84.5 ± 1.0	33.1 ± 0.9	117.6 ± 0.9	490 ± 57	249 ± 12	323 ± 10 ^b
Distal PF						
Control 1	-84.6 ± 1.0	37.5 ± 0.9	122.1 ± 1.2	475 ± 60	204 ± 6	247 ± 8
1.0 mM ENF	-83.2 ± 0.7	34.8 ± 1.0 ^a	118.0 ± 1.6 ^a	423 ± 74	153 ± 6 ^a	229 ± 3 ^a
Control 3	-82.6 ± 0.7	35.3 ± 0.9 ^b	118.0 ± 1.4 ^b	431 ± 74	204 ± 2	257 ± 3 ^b
0.6 mM ENF	-83.1 ± 1.1	36.9 ± 0.7	120.0 ± 1.2	419 ± 48	187 ± 5 ^a	255 ± 4 ^a
Control 5	-82.9 ± 1.0	35.0 ± 1.2 ^b	117.9 ± 1.4 ^b	421 ± 79	209 ± 5 ^b	264 ± 3 ^b

MDP, maximum diastolic potential; OS, overshoot; Amp, amplitude; \dot{V}_{max} , rate of phase 0 depolarization; APD, action potential duration at 50% and at 90% repolarization; PF, Purkinje fibers; HAL, halothane; ISO, isoflurane; ENF, enflurane.

Values are expressed as mean ± SEM for six hearts in each group based on pooled values from 10 Purkinje fibers for each region under each condition.

^a*P* ≤ 0.05 versus immediate preceding control.

^b*P* ≤ 0.05 versus initial control (control 1), time-dependent effect.

Repolarization Characteristics

The anesthetics produced substantial decreases of APD as illustrated in Figure 2. Qualitatively, each anesthetic produced larger reductions of proximal fiber APD than of distal fiber APD and thereby tended to reduce the difference of APD between fibers in the two regions present under control conditions. In addition, the decreases of proximal fiber APD in response to enflurane and isoflurane appeared more prominent than in response to halothane. Quantitatively, the recording location, group, and time or dose effects were each

associated with a significant influence on the values of APD obtained at each level (50%–95%) of repolarization. The regional difference was characterized by greater (*P* ≤ 0.01) mean values of proximal than of distal fiber APD at each level of repolarization in the absence of anesthetic in all groups. There were usually significant time-dependent increases of the mean values of APD between the initial (C1), or middle (C3), and final (C5) control periods in each anesthetic group (Table 1) as well as in the no-anesthetic control group (data not shown). The control difference between prox-

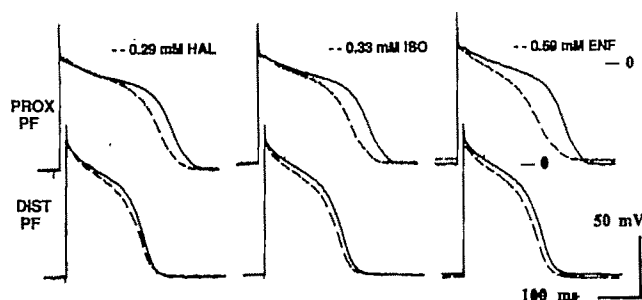


Figure 2. Simultaneously recorded single proximal (PROX) and distal (DIST) Purkinje fiber action potentials from typical preparations under control conditions (solid tracings) and after exposure (dashed tracings) to halothane (HAL), isoflurane (ISO), and enflurane (ENF). Each anesthetic produces a larger decrease of proximal than distal fiber APD.

imal and distal APD_{90} values, averaging 68 ± 10 ms for all groups (time-averaged values; proximal 320 ± 16 ms vs distal 252 ± 11 ms; $P \leq 0.01$) was well maintained during superfusion but decreased from 75 ± 9 ms to 65 ± 11 ms between initial and final control periods in association with slight increases of both proximal and distal APD_{90} . To minimize the influence of time-dependent changes on the assessment of anesthetic effects, the change of APD from immediate preceding control values was calculated for each region and anesthetic concentration and at analogous times in the no-anesthetic group. The resulting changes were used to evaluate dose dependence and differences by regions for each dose within anesthetic groups and to compare responses between groups based on the variance of all preparations.

For either proximal or distal fibers, the changes of APD were larger ($P \leq 0.01$) at the high concentration compared with the low concentration of each anesthetic (Figure 3). In addition, for either dose of the anesthetics, the changes of APD were larger ($P \leq 0.01$) in the proximal than in distal fibers. To clarify between-group comparisons, only those changes that were significantly larger than the changes at the same time in the no-anesthetic group are indicated in Figure 3. For proximal fibers at high dose, the decreases of APD resulting from 1.0 mM enflurane were larger (APD_{50}) or equal to (APD_{90}) that resulting from 0.8 mM isoflurane, and both anesthetics decreased APD more than halothane did ($P \leq 0.01$). For distal fibers at high dose, enflurane and isoflurane decreased APD_{50} more than halothane did ($P \leq 0.05$). However, the smaller change of APD_{50} resulting from halothane (-12 ± 7 ms) was not significantly larger than the change (-3 ± 7 ms) occurring at the same time in the no-anesthetic group, and thus 0.7 mM halothane may not significantly depress distal fiber APD_{50} . Similarly, only the decrease of distal fiber APD_{90} resulting from 0.8 mM isoflurane (-25 ± 9 ms) was larger ($P \leq 0.05$) than the change in

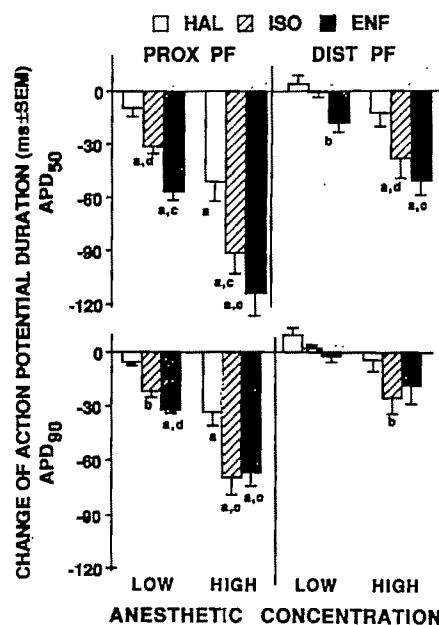


Figure 3. Between-group comparisons of changes of APD of proximal and distal Purkinje fibers on exposure to low and high doses of halothane (0.3 and 0.7 mM), isoflurane (0.4 and 0.8 mM), and enflurane (0.6 and 1.0 mM). a, $P \leq 0.01$; b, $P \leq 0.05$ compared with changes in the no-anesthetic (time control) group. c, $P \leq 0.01$, d, $P \leq 0.05$ compared with changes in the halothane group.

the no-anesthetic group (-2 ± 6 ms), whereas the changes resulting from enflurane (-18 ± 10 ms) and halothane (-4 ± 7 ms) did not differ from that in the no-anesthetic control group. These comparisons, based on changes, exhibited greater between-group variations than the mean values under each condition. Thus, although the small decreases of proximal fiber APD_{50} and APD_{90} resulting from low-dose halothane (Figure 3) were not significant relative to the changes in the no-anesthetic group, the mean values of proximal fiber APD_{50} (231 ± 4 ms) and APD_{90} (299 ± 6 ms) in the presence of halothane (Table 1) were significantly less ($P \leq 0.05$) than the mean values of the preceding and following controls (APD_{50} : C3 241 ± 6 ms, C5 251 ± 6 ms; APD_{90} : C3 305 ± 6 ms, C5 314 ± 6 ms) within the halothane group.

The results shown in Figure 3 generally indicate that the decreases of APD in fibers of either region were larger for 1.0 mM enflurane and 0.8 mM isoflurane than for 0.7 mM halothane and that the anesthetic actions tended to be greater for early (APD_{50}) compared with later (APD_{90}) repolarization. The actions of the agents decreasing APD_{50} and APD_{90} in the more sensitive proximal fibers are illustrated in Figure 4 as a function of the millimolar concentrations and of the calculated MAC multiples. Expressed as millimolar concentration, isoflurane and enflurane produced about equivalent decreases of APD at concentrations less than the higher halothane dose. In

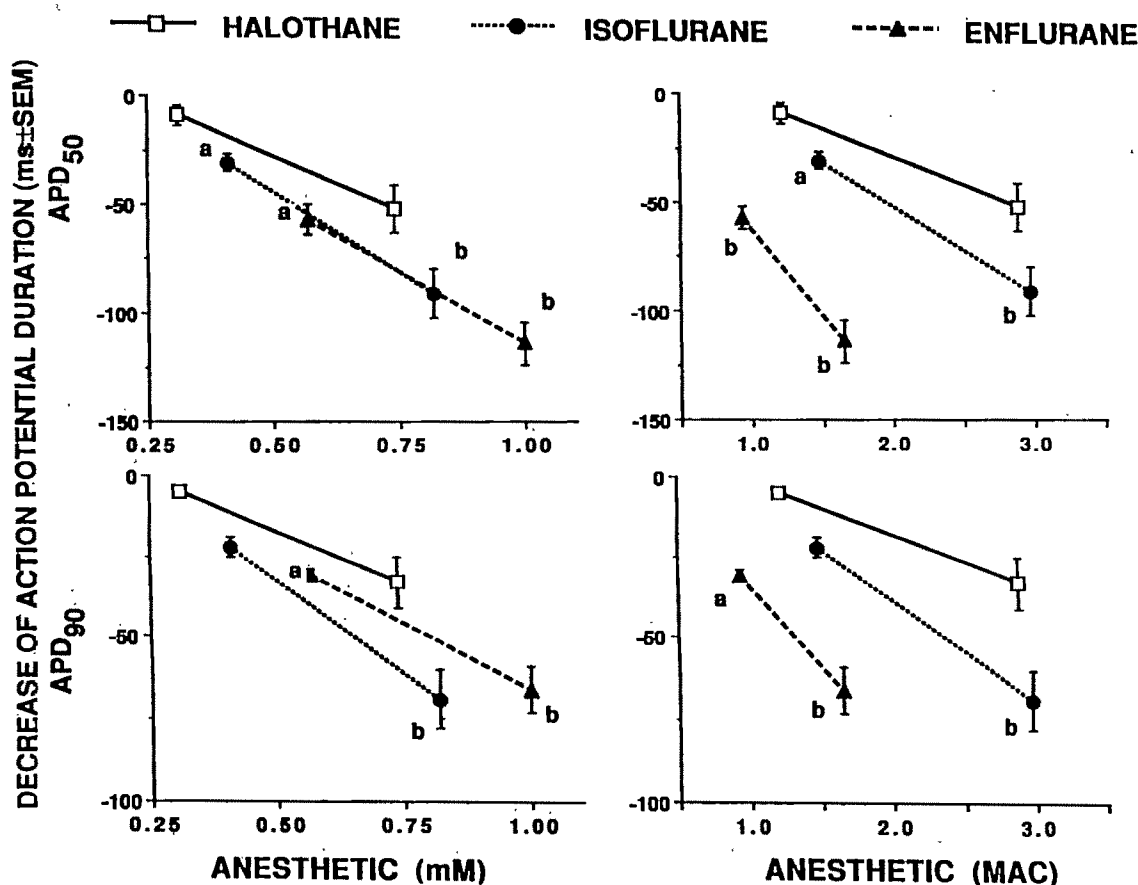


Figure 4. Decreases of proximal Purkinje fiber APD₅₀ and APD₉₀ (y-axes) as a function of millimolar and MAC (minimum alveolar concentration) anesthetic concentrations (x-axes). a, $P \leq 0.05$ vs low-dose halothane, b, $P \leq 0.01$ versus high-dose halothane.

terms of MAC multiples, enflurane produced larger decreases of APD than isoflurane or halothane did at somewhat less than equianesthetic doses, and high-dose isoflurane produced larger decreases of APD₅₀ and APD₉₀ than did an approximately equianesthetic concentration of halothane.

The larger actions of each anesthetic on proximal than or distal fiber APD (Fig. 2) tended to reduce the difference of APD between the two regions present under control conditions. This aspect of anesthetic action is summarized in Figure 5 by derived values of the difference of APD₉₀ between fibers of the two regions under initial control conditions and in the presence of the higher concentration of each agent. Halothane, isoflurane, and enflurane each reduced the difference between the values of APD₉₀ in the two regions. Although high-dose enflurane and isoflurane decreased APD₉₀ in proximal fibers more than halothane did, these anesthetics were not significantly more effective than halothane in reducing the difference of APD₉₀ between the two regions, probably because enflurane and isoflurane also tended to decrease distal fiber APD₉₀.

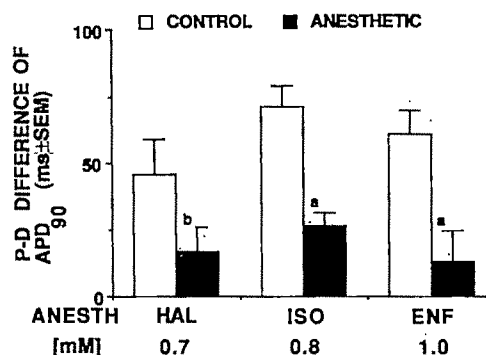


Figure 5. Differences of APD₉₀ between proximal and distal Purkinje fibers under control conditions and at the higher doses of halothane, isoflurane, and enflurane. Each anesthetic reduced regional differences of APD₉₀. a, $P \leq 0.01$, b, $P \leq 0.05$ compared with changes in the no-anesthetic control group.

Discussion

Our findings indicate that all three anesthetics have greater actions decreasing APD of Purkinje fibers exhibiting characteristically long (proximal fibers) rather than short (distal fibers) APD. These actions

reduce the normal regional difference of APD (proximal longer than distal) present under control conditions in the canine heart. In addition, isoflurane and especially enflurane produce larger decreases of proximal fiber APD than halothane does at lower (enflurane) or approximately equivalent (isoflurane) multiples of equianesthetic (MAC) doses. Thus, the relative anesthetic actions on Purkinje fiber repolarization (enflurane \geq isoflurane $>$ halothane) appear to differ from their relative anesthetic potencies (halothane $>$ isoflurane $>$ enflurane) and their commonly accepted relative negative inotropic effects (halothane = enflurane $>$ isoflurane) on isolated muscle fibers (13-15).

Low concentrations of halothane, isoflurane, and enflurane (1 MAC) produce comparatively similar decreases of spontaneous rate, phase 4 diastolic depolarization and APD_{50} of primary pacemaker fibers in the guinea pig sinoatrial node (16). Although other studies indicate that relatively larger concentrations of these anesthetics are required to decrease APD_{90} of ventricular muscle fibers (17-21), these anesthetics are not known to differ in their effects on the action potential contour in this tissue. The differential regional actions of isoflurane and enflurane on canine Purkinje fiber repolarization observed in the present study were similar to but more prominent than those previously found for halothane (4,6). The findings suggest that anesthetic actions shortening Purkinje fiber APD_{90} may occur at relatively low concentrations in those regions of the conduction system (false tendons) exhibiting characteristically longer control APD, with minimal effects on the maximum diastolic potential, the amplitude, or \dot{V}_{max} of the action potential.

The results are necessarily limited because of the artificial conditions of superfusion of large endocardial preparations in which only several subendocardial cell layers maintain normal action potentials, whereas deeper hypoxic myocardial fibers gradually depolarize and become electrically quiescent. The time-dependent increases of distal fiber APD observed may reflect the electrotonic influence of their connections through low-resistance Purkinje fiber-muscle junctions to progressively more depolarized myocardial fibers during continued superfusion. The *in vitro* findings are also limited in their extrapolation to the *in vivo* state in which anesthetic-related changes in hemodynamics, ventricular volume, humoral factors, or cardiac autonomic efferent activity (22) could influence the repolarization characteristics of Purkinje fibers in different conduction pathways through the ventricular conduction system.

The mechanisms by which the volatile anesthetics alter the Purkinje fiber action potential probably involve several simultaneous changes in different

transmembrane ionic currents and underlying specific channel (Ca^{2+} , Na^{+} , K^{+}) activities. In addition, the action potentials of Purkinje fibers clearly differ in different regions of the heart and also differ from those of ventricular muscle fibers. These tissue and regional differences may reflect specific cellular characteristics such as the absence (Purkinje) or presence (ventricular muscle) of T-tubules, differences in passive membrane properties, or differences in the number, density, and activity of specific channel types between tissues or regions. Studies from this laboratory indicate that halothane, isoflurane, and enflurane produce similar reductions of inward Ca^{2+} channel current in Purkinje fibers (23). In addition, halothane and isoflurane similarly inhibit the small fraction of inward Na^{+} current that persists several hundreds of milliseconds after depolarization and contributes to maintenance of the prolonged plateau duration of false tendon Purkinje fibers (24). These actions on plateau-phase Na^{+} currents may account for the similarity between the regional actions of halothane and the low doses of the Na^{+} channel blocker tetrodotoxin on the APD of proximal and distal Purkinje fibers (6). However, if they are quantitatively similar they may not account for the apparent greater potency of isoflurane than of halothane in decreasing APD. It is also possible, although less likely, that the volatile anesthetics could produce different degrees of action potential shortening because of use-dependent block of either Na^{+} or Ca^{2+} channels. On the other hand, there is evidence that halothane may inhibit outward K^{+} current, at least in atrial fibers (25), and may have actions on Na^{+} - Ca^{2+} exchange currents (18) during either early or later repolarization. Thus, the actions of the anesthetics on the transmembrane ionic currents underlying generation of the cardiac action potential are complex and require further careful studies to quantitatively account for the observed differences in their regional effects on Purkinje fiber APD.

The actions of the volatile anesthetics reducing the difference between the APD_{90} of false tendon and apical Purkinje fiber may alter conduction during the relative refractory period and potentially influence the occurrence of reentrant excitation. Early premature impulses descending through the atrioventricular node normally undergo conduction block at regions of increased APD and refractoriness in the bundle branches, producing functional bundle branch block (26). The actions of isoflurane and enflurane decreasing the APD_{90} false tendon fiber may be expected to reduce refractory periods in the His-Purkinje system *in vivo* in a manner similar to that reported for halothane (7) and to increase the prematurity required to produce aberrant conduction. These actions could contribute to reexcitation by

(a) permitting conduction of premature descending impulses, which would otherwise undergo conduction block along some pathways, to a wider region of the more slowly conducting and incompletely repolarized endocardium, or by (b) decreasing the APD of Purkinje fibers proximal to a site of unidirectional block such that a potential reentrant impulse would not have to persist as long in its retrograde conduction to the site of block before expiration of the proximal refractory period. The latter type of action may contribute to the facilitation of reentrant activity by halothane in the 1-day-old canine infarction model in which the decreases of APD of false tendon fibers located outside the ischemic region by halothane may permit reexcitation by slowly conducting impulses within the more refractory ischemic region (4). On the other hand, isoflurane and enflurane, which are less "sensitizing" to the arrhythmogenic actions of catecholamines than halothane (27), were observed to produce larger decreases of false tendon Purkinje fiber APD than halothane did. If the combination of epinephrine with halothane slows conduction in false tendon Purkinje fibers and contributes to conduction block and reentry, as has been suggested by Reynolds and Chiz (28), and either the α - or β -adrenergic effects of catecholamines on Purkinje fibers (29) contribute to reexcitation by increasing the disparity of regional repolarization characteristics in the conduction system, then isoflurane or enflurane could be less "sensitizing" than halothane because the latter produces relatively smaller decreases of Purkinje fiber APD in specific regions of the heart. This speculation would suggest that very low concentrations of halothane may produce "sensitization," with perhaps some change at higher doses. Metz and Maze (30) reported that the threshold dose for epinephrine-induced arrhythmias in the dog is not altered over a range of halothane concentrations from 0.5 to 2.0 vol%. In contrast, other studies suggest that subanesthetic concentrations of halothane (0.1–0.5 vol%) produce dose-dependent reduction of the arrhythmogenic plasma level of epinephrine, in the presence of etomidate basal anesthesia (31). However, the possible relationship between the observed differences in the actions of halothane, isoflurane, and enflurane on the APD₉₀ of false tendon Purkinje fiber and the differences between their actions altering the sensitivity of the heart to the occurrence of catecholamine-associated arrhythmias is unknown.

In conclusion, we demonstrate that isoflurane and enflurane, like halothane, produce dose-dependent regional effects on Purkinje fiber action potentials characterized by larger decreases of APD in fibers exhibiting long (false tendon fibers) as compared with short (apical fibers) control durations. Isoflurane

and enflurane are "more potent" than halothane in decreasing APD of the more sensitive false tendon fibers. These actions of the volatile anesthetics reduce regional differences of Purkinje fiber APD and could alter the occurrence of arrhythmias in the ventricular conduction system when the latter are associated with abnormal conduction and differences in the refractory characteristics of fibers in different regions.

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Effect of Midazolam on the Auditory Event-Related Potential: Measures of Selective Attention

Ruth A. Reinsel, PhD, Robert A. Veselis, MD, Riitta Heino, MD, Saul Miodownik, MEE, Ramdas Alagesan, FFARCS, and Robert F. Bedford, MD

Memorial Sloan-Kettering Cancer Center, Department of Anesthesiology and Critical Care Medicine, New York, New York

To elucidate the delayed effects of midazolam, we assessed electrophysiologic and motor responses by measuring auditory event-related potentials and a button-press reaction time response in 10 normal volunteers (aged 25–36 yr). Fifty minutes after intravenous infusion of 0.07 mg/kg of midazolam, subjects were mildly sedated, oriented, and readily responsive to verbal commands. To obtain ERPs, frequent tones (85%: 1000 Hz) and rare tones (15%: 2500 Hz) were presented at intervals of 1.5 s. Electroencephalographic signals were collected from F_z, C_z, and P_z for 1000 ms after stimulus presentation until 40 artifact-free rare-tone responses were obtained (average time, 6 min). Peak-to-peak amplitudes and latencies for N2, P3, and the subsequent negative slow wave (N3) were averaged within condition and were analyzed by repeated measures analysis of variance.

After midazolam infusion, there was a 50% decrease in amplitude of P3 in response to target tones ($P < 0.006$), whereas N3 latency increased by 40 ms ($P < 0.05$). Event-related potential amplitudes were still significantly larger to rare (target) stimuli ($P < 0.003$) after midazolam infusion. Although reaction time increased by 70 ms ($P = 0.031$), performance accuracy remained unchanged. Self-ratings of sleepiness and concentration show that a significant sedation effect was still present 50 min after infusion. Although routine clinical examination may be normal, full recovery from the effects of a typical intravenous dose of midazolam requires more than 50 min. The potential for adverse drug interaction, particularly with narcotics, is still present at this time.

(Anesth Analg 1991;73:612–8)

Midazolam is a short-acting benzodiazepine used for sedation and for the production of anterograde amnesia (1,2). A 5-mg intravenous dose in a 70-kg adult will produce amnesia lasting 20–30 min (3). Midazolam is frequently used in this dose range to provide sedation during minor operative procedures. Customarily, patients are observed closely for 30–60 min after intravenous administration of midazolam and then they are discharged from medical care shortly thereafter. Gross clinical examination and behavioral responses may lead to the conclusion that there are no residual effects of midazolam. More sensitive tests, however, may show a continuing degradation of performance (4), and this subclinical effect may be greatly enhanced by

small doses of other drugs acting on the central nervous system (CNS) especially narcotics (5,6).

Benzodiazepines produce dramatic changes in CNS activity, as demonstrated by the electroencephalogram (EEG) (7–9). Long-latency event-related potentials (ERPs) obtained from the raw EEG can provide information on higher cognitive processing. These potentials are elicited by tasks requiring attention, and thus would be affected by agents impairing attention including benzodiazepines (10). The late components of the ERP, which include N2 (or N200) and P3 (or P300), specifically index stages in the deployment of selective attention (11–14).

Although other varieties of evoked potentials have drawn attention in the anesthesia literature (15,16), few studies have investigated the effects of benzodiazepine sedation on the late components of the ERPs including P3. Conditions that reduce the efficiency of CNS transmission and cognitive information processing, such as sleep, CNS depressants, and organic dementia reduce the amplitude and increase the latency of the P3 component (17–19).

In this study, we focused our attention on the late

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Address correspondence to Dr. Reinsel, Memorial Sloan-Kettering Cancer Center, Department of Anesthesiology and Critical Care Medicine, 1275 York Avenue, New York, NY 10021.

components of the auditory ERP as sensitive indicators of complex cognitive processing, and we report the changes observed approximately 50 min after intravenous infusion of midazolam in volunteer subjects. Concomitantly, behavioral data (reaction time and subject visual analogue scales (VAS)) were obtained to assess the sedative effects of midazolam. This study is different from those of previous reports in that midazolam was administered in a fashion that would be more typical of a clinical situation (20,21). Midazolam was given in a single dose, with only two ERP recordings obtained at 45 and 60 min after drug administration, to minimize any fatigue or practice ("habituation") effects on ERP results (22). This time corresponds to when most patients would be released from close observation after a minor operative procedure.

Methods

Ten paid volunteers (4 men, 6 women) aged 25–36 yr (mean age, 30.4 yr) gave their informed consent to participate in this protocol approved by the local institutional review board. Subjects had a negative history for medical or neurologic problems. Subjects had no oral intake for at least 8 h and were allowed no caffeine on the day of the study.

An intravenous infusion of midazolam (0.07 mg/kg) was administered over a 10-min period. At the end of infusion, the subjects were drowsy but still responsive to verbal commands. During and after the infusion, subjects were monitored with electrocardiogram, arterial blood pressure, and pulse oximetry.

As a measure of replicability, ERPs were recorded twice in the baseline period, and again at 45 and 60 min after the start of the infusion. Subjects were instructed to keep their eyes closed and to avoid talking or moving during recording. The analog EEG signal was collected from F_Z, C_Z, and P_Z referenced to linked mastoids (A₁ and A₂) for 1000 ms after stimulus presentation. Electrode impedances were less than 5 K Ω . Using a Tracor Northern Nomad 3400 acquisition device with on-line artifact rejection, the EEG was sampled at 128 Hz in a bandwidth of 1–30 Hz. Auditory stimuli were presented using an "oddball" paradigm, with frequent (85%: 1000 Hz) and rare (15%: 2500 Hz) tones presented at intervals of 1.5 s. Tones had a stimulus duration of 60 ms and were presented binaurally at 80 dB without masking noise. Electroencephalogram responses to the stimulus tones were summed and averaged by the Tracor Nomad 3400. Each ERP recording ("trial") took about 6 min and was terminated when 40 artifact-free rare-tone responses had been collected.

Subjects were instructed to count the rare tones (targets) and to press a button every time a rare tone

was presented. Frequent tones (nontargets) were not task-relevant. After the conclusion of ERP recording, subjects were asked to report how many rare tones they had counted. They did not receive feedback on the accuracy of their count.

Stimulus tones and button-press responses were recorded on separate channels of a stereo cassette recorder. The time delay between stimulus tone and button-press response was then determined using the same recorder in the playback mode. An interface circuit using two phase-locked loop tone decoders was used to differentiate between the frequent and rare tones on the stimulus channel of the tape. A separate detector circuit determined the timing of the button-press response. Digital outputs from both circuits were connected to a timer interface board (model CTM-05; Keithly/Metrabyte, Taunton, Mass.) residing within a PC-AT 386 clone computer. Software written by one of the authors (S.M.) determined the time delay between the stimuli and the responses. To verify periodically the accuracy of the reaction time (RT) analysis system, a calibration tape was recorded containing a set of tones and responses with known delays between 10 and 990 ms. The time delay accuracy so calculated was reliable to within ± 10 ms.

The RT was measured in milliseconds, and incorrect responses (pushing button when rare tone was not presented; no button push within 1 s after rare tone) were counted. The mean RT for each trial was later correlated with mean peak latency and with amplitude of the individual components of the ERP for that trial.

Subjective ratings of sleepiness (SLP) and concentration (CON) were obtained at frequent intervals throughout the study. These ratings were made by placing a mark on a 15-cm line between two anchored extremes [very wide awake—very sleepy; can't concentrate at all—can concentrate fully]. The data were scored as the distance in centimeters from the zero point of the scale to the subject's mark. Visual analogue scale ratings made before and after the ERP recordings were averaged and compared with the mean baseline VAS ratings by paired *t*-test.

A serum sample was obtained at the end of each ERP recording to determine midazolam concentration. As the two ERP trials made after receiving midazolam were averaged together, the two serum levels were also averaged for each subject.

For each average waveform, the components N2, P3, and N3 (the negative-going slow wave following P3) were identified visually. The latency and amplitude for each component were determined by cursor placement on the ERP display provided by the Tracor Nomad 3400. Latency was measured in milliseconds from stimulus onset to the point of maximum ampli-

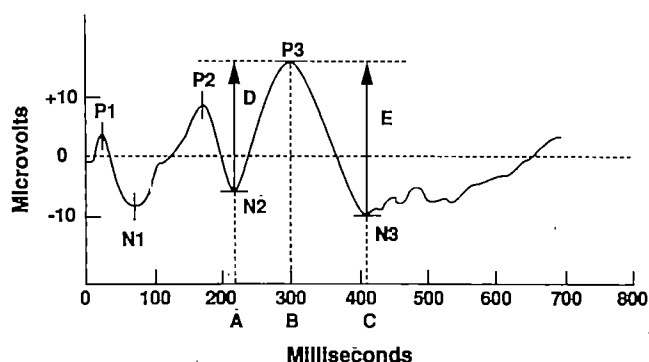


Figure 1. Schematic representation of an auditory event-related potential showing positive and negative peaks labeled successively P1, N1, P2, N2, P3, and N3. A, B, and C identify the latency of peaks N2, P3, and N3, respectively. D and E show the measurement of amplitude for N2P3 and P3N3, respectively.

tude. Amplitude was measured peak-to-peak and was defined as the point of maximum positivity (or negativity) for that component. Figure 1 shows how latency and amplitude are obtained for each waveform component. Measurements of peak amplitudes and latencies for the two trials in each condition were compared by paired *t*-test. As no significant differences were found, the two trials were averaged for each condition. A repeated measures analysis of variance was computed for each ERP component (N2, P3, and N3 latency; N2P3 and P3N3 amplitude). The analysis included the main effects of condition (Cond, baseline vs drug), stimulus (Stim, target vs nontarget), electrode (Elec; F_z, C_z, P_z), and their interactions. Probability values less than 0.05 were taken as significant. All statistical analyses were conducted with the SAS package (SAS release 6.03; SAS Institute Inc., Cary, N.C.).

Results

The major effect of midazolam on the ERP is a reduction in the amplitude of the P3 waveform (Figure 2). P3N3 amplitude decreased nearly 50% after midazolam infusion in response to target tones, whereas amplitudes to nontarget tones were unaffected (Cond: $P < 0.0001$; Stim: $P < 0.0001$; Cond/Stim interaction: $P < 0.006$) (Table 1 and Figure 3). N2P3 amplitude was unchanged after midazolam infusion, with target tones continuing to elicit higher amplitudes after infusion (Stim: $P < 0.003$).

Midazolam had little effect on peak latency (Table 2). N2 latency to target stimuli increased slightly after midazolam infusion (about 18–29 ms), whereas nontarget stimuli were unchanged (Cond/Stim interaction: $P < 0.04$). N3 latency increased by 40 ms ($P < 0.05$) for both target and nontarget stimuli.

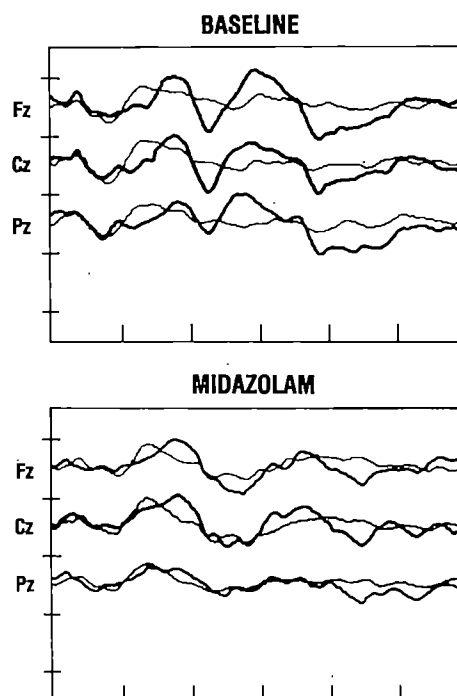


Figure 2. Event-related potential (ERP) waveforms from a representative subject (S No. 5) before and after midazolam administration. Waveforms are recorded from F_z, C_z, and P_z referenced to linked mastoids. The time after stimulus presentation is represented on the x-axis in units of 100 ms per division. The dark line represents the averaged auditory ERP obtained for the (rare) target stimuli, the lighter line represents the averaged ERP obtained for the (frequent) nontarget stimuli. In the baseline condition, N2 and P3 are clearly visible to target stimuli. Note the reduction in amplitude of P3N3 in all channels after midazolam.

As shown in Figure 3, significant variations in N2P3 amplitude were found between recording sites (Elec: $P < 0.005$) with the largest effect of midazolam occurring at P_z (Elec/Stim interaction: $P < 0.002$). No significant differences were found between measurement sites for P3N3 amplitude. The P3 elicited by target tones had a shorter latency at the P_z electrode in both conditions (Elec/Stim interaction: $P < 0.002$). No significant latency differences were found between electrode sites for any other peaks of the waveform before or after the administration of midazolam.

Sleepiness increased and concentration decreased markedly during drug administration, reaching their maximum about 1 h after the infusion ended (Figure 4). Visual analogue scale scores obtained with the ERP recordings 45–60 min after infusion showed a significant increase in sleepiness ($P < 0.008$) and a decrease in concentration ($P < 0.02$) compared with the mean baseline levels. Self-ratings of sleepiness and concentration taken at various points during the study were highly intercorrelated ($-0.75 < r < -0.93$). These high intercorrelations indicate that the

Table 1. Amplitude of Event-Related Potential Components

Component and electrode	Baseline (μ V)	Midazolam (μ V)
N2P3		
Frontal		
Nontargets	2.87 \pm 1.92	3.48 \pm 2.28
Targets	10.03 \pm 5.71	9.22 \pm 4.75
Central		
Nontargets	3.27 \pm 1.88	3.40 \pm 2.39
Targets	8.61 \pm 4.57	8.23 \pm 5.35
Parietal		
Nontargets	2.50 \pm 0.90	2.24 \pm 1.42
Targets	7.31 \pm 3.60	5.82 \pm 4.39
P3N3		
Frontal		
Nontargets	4.18 \pm 3.35	3.30 \pm 1.35
Targets	15.09 \pm 5.73	7.52 \pm 2.74
Central		
Nontargets	4.30 \pm 2.76	3.12 \pm 1.12
Targets	15.80 \pm 5.67	8.37 \pm 3.28
Parietal		
Nontargets	3.80 \pm 1.63	2.49 \pm 0.81
Targets	16.06 \pm 4.38	9.09 \pm 3.53

Values are mean \pm SD.

two VAS scales are reliably measuring the same underlying cognitive dimension, sedation.

The RT data were available for seven subjects. Subjects correctly counted 95% of the rare tones during baseline and 92% after sedation. As shown in Table 3, RT increased an average of 68 ms after midazolam administration ($P = 0.031$), but performance accuracy remained unchanged; that is, there was no increase in the number of misses (failure to respond to target stimuli) or of false alarms (responses made to nontarget stimuli).

The mean (\pm SEM) of serum midazolam concentrations obtained after the second set of ERP recordings was 34.3 ± 3.5 μ g/mL. Values ranged from 56 to 17 μ g/mL (Table 4). Although correlations of serum midazolam concentrations with both ERP latencies and amplitudes were of moderate size, they did not reach statistical significance.

Discussion

The late components of the ERP correspond with reaction to and cognitive processing of a stimulus (9,10). The N2 (or N200) component occurs from 200 to 300 ms after stimulus, and the P3 (or P300) occurs from 300 to 400 ms after stimulus. The N2 wave is thought to reflect a stage of information processing associated with stimulus evaluation, particularly "mismatch" from expectation (23). The P3 is thought to represent a "template updating" process in short-term memory whereby, on occurrence of a deviant

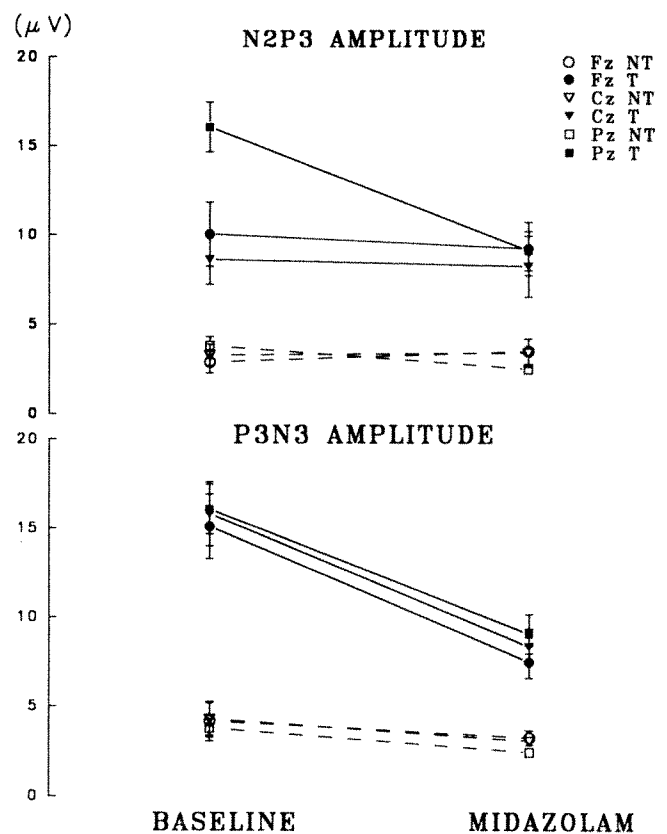


Figure 3. Amplitude of N2P3 and P3N3 to target (T) and nontarget (NT) stimuli before and after midazolam administration as a function of electrode location. Note that target stimuli elicit higher amplitudes than nontargets in both conditions. N2P3 is relatively unaffected by midazolam, whereas midazolam reduces P3N3 amplitude to target stimuli.

stimulus, the cognitive model of the external stimulus environment is revised (24). The magnitudes of these components vary depending on the nature of the stimulus/task demands. Generally, the N2 and the P3 waves are elicited by the same experimental paradigm—attention to an infrequent stimulus associated with task performance (8). The P3 is of particular interest because it is sensitive to cognitive functions and to instructional manipulations rather than to physical parameters of the stimulus (25,26). We found that indeed the N2 was of shorter latency and higher amplitude to the less-frequent target stimuli and that the P3 was elicited only to the rare tones, which required a button-press response from the subject.

It is interesting to note that the N2P3 amplitude did not change, whereas the P3N3 amplitude was strongly affected. This would imply that mismatch detection was intact, as shown by the accurate behavioral response, but that little effort was put into the template updating process. This lack of memory updating may represent a manifestation of the amnesic effect of midazolam and may have a clinical

Table 2. Latency of Event-Related Potential Components

Component and electrode	Baseline (ms)	Midazolam (ms)
N2		
Frontal		
Nontargets	264.7 ± 31.6	260.0 ± 26.3
Targets	231.2 ± 25.1	254.8 ± 30.9
Central		
Nontargets	264.7 ± 29.6	262.1 ± 23.0
Targets	224.6 ± 31.2	253.6 ± 27.7
Parietal		
Nontargets	264.1 ± 30.0	256.0 ± 21.3
Targets	222.1 ± 29.4	249.6 ± 35.3
P3		
Frontal		
Nontargets	316.1 ± 44.1	350.6 ± 79.6
Targets	302.0 ± 28.3	363.6 ± 103.5
Central		
Nontargets	318.3 ± 44.9	352.3 ± 90.8
Targets	293.1 ± 31.7	354.6 ± 105.0
Parietal		
Nontargets	316.1 ± 41.2	355.3 ± 99.7
Targets	274.4 ± 25.6	340.3 ± 112.9
N3		
Frontal		
Nontargets	388.8 ± 52.4	436.7 ± 86.4
Targets	420.5 ± 28.4	462.8 ± 82.2
Central		
Nontargets	383.0 ± 48.2	444.2 ± 95.1
Targets	410.1 ± 22.2	458.7 ± 80.9
Parietal		
Nontargets	384.0 ± 39.9	445.6 ± 84.9
Targets	414.7 ± 24.5	459.2 ± 80.1

Values are mean ± SD.

correlate in the frequently observed tendency of patients to ask the same question repeatedly after midazolam administration. In a recent study with fentanyl and isoflurane or nitrous oxide anesthesia, Plourde and Picton (27) found that although no clear P3 wave could be demonstrated during emergence from anesthesia, the P3 response had returned by 41 min after extubation (on the average). They suggest that the reappearance of the P3 indicates that at this point in the recovery from anesthesia the patient has regained full consciousness in the sense of "the ability to think about what one knows or perceives." The use of the P3 in this fashion underlines its potential usefulness as a measure of recovery from anesthesia.

Three prior investigations have examined the effects of benzodiazepines on the late components of the auditory ERP. Samra et al. (28) reported a decrease in P3 amplitude and an increase in P3 latency after intravenous lorazepam was given in a dose inducing light sedation. They interpreted these changes as the result of generalized sedation, as the decrease in P3 amplitude did not differ between secobarbital and lorazepam. Milligan et al. (20) re-

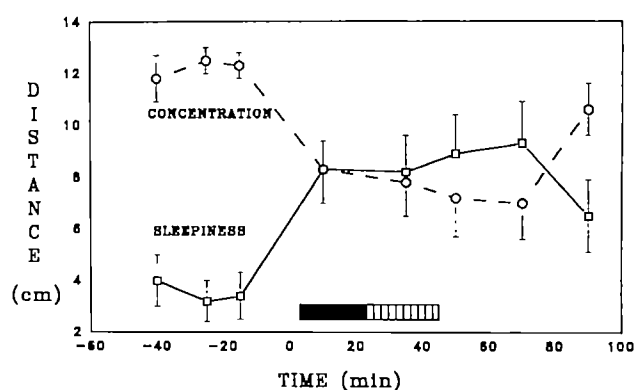


Figure 4. Subjective ratings (mean ± SEM) of sleepiness and concentration before, during, and after midazolam infusion. The filled portion of the bar above the x-axis indicates the duration of complete amnesia; the striped portion indicates the duration of partial amnesia. Note the large change in subjective rating during and immediately after infusion. The degree of self-reported effect remains fairly constant after this throughout most of the experiment, although cognitive and EEG effects are changing. (Reproduced by permission of J.B. Lippincott & Co.: Veselis RA, Reinse R, Alagesan R, Herno R, Bedford RF. The EEG as a monitor of midazolam amnesia: Changes in power and topography as a function of amnesic state. *Anesthesiology* 1991;74:866-74.)

Table 3. Behavioral Performance Under Midazolam Sedation

Variable	Baseline	Midazolam
Mean reaction time (ms)	291.1 ± 41.8	359.1 ± 75.3*
Target tones correctly counted (%)	95.1 ± 7.9	92.4 ± 13.8

Values are mean ± SD.

*P < 0.05.

ported a decrease in the amplitude of the P3, which continued for 5 h (five tests) after an intravenous infusion of 0.3 mg/kg of midazolam. This dose was much larger than that used either in this study or in a typical clinical setting. As data were gathered for 6 h, some effects on the P3 may have been related to fatigue, as demonstrated by the placebo response over 4 h of testing in Samra's study. Domino et al. (21) also reported a decrease in P3 amplitude after the administration of midazolam in incremental doses of 0.02 mg/kg each. There was a simultaneous reduction from 99% to 77% in accuracy of counting the rare tones. The placebo arm of that study did not demonstrate a fatigue effect over the short duration (60 min) of that study.

In our study, the ERP peak latencies were not strongly affected by midazolam 50 min after its administration. Prolongation of ERP latencies is usually a very sensitive sign of drug effect, but our results indicate that ERP latencies may not be as sensitive as amplitude changes to the presence of midazolam. At equivalent serum levels, Milligan et al. (20) found no significant effects on the ERPs.

It should be noted that measurements of P3 am-

Table 4. Serum Levels of Midazolam at the Time of Recording of the Two Event-Related Potential Trials (ERP3 and ERP4) and Their Average Value

Subject	Midazolam serum levels ($\mu\text{g/mL}$)		
	ERP3	ERP4	Average ^a
1	45	—	45
2	53	33	43
3	26	20	23
4	38	32	35
5	56	44	50
6	30	27	28.5
7	38	30	34
8	55	32	43.5
9	17	17	17
10	22	26	24
Mean ($\mu\text{g/mL}$)	38.0	29.0	34.3
SEM	4.5	2.6	3.5

ERP, event-related potential.

^aAverage values were used in the computation of correlations with ERP latencies and amplitudes.

plitude are not standardized; thus, comparisons between different studies may not be valid. Frequently amplitude is measured as a difference between the average baseline before stimulus presentation and the waveform peak; the average amplitude across a given latency interval may also be used (as in the study by Plourde and Picton). Alternatively, peak-to-peak amplitude differences are reported. This method involves measurements of two components, each of which may change independently of the other. Samra et al. measured P3 peak-to-peak, analogous to our P3N3 amplitude. Milligan et al. and Domino et al. did not report on their method of measurement of P3 amplitude. We describe our results both in terms of N2P3 and P3N3 amplitudes to identify precisely the ERP component in question. Indeed, we found that waveform components do change independently: midazolam substantially decreased P3N3 amplitude without affecting N2P3 amplitude.

The accurate discrimination between target and nontarget stimuli was maintained under the influence of midazolam, with targets eliciting higher P3 amplitudes both before and after sedation. Midazolam preferentially affected the P3 response to target stimuli (Figure 3). This amplitude is highly sensitive to motivational factors (26), and the decrease in amplitude can be interpreted as a sign of lessened effort, with fewer cognitive resources being brought to bear on a task (29). Despite subjects' self-reports of lessened concentration at this time, they accurately performed the button-press task with a slightly prolonged (70 ms, $P < 0.05$) RT. The increase in RT (from 291 to 359 ms) was not echoed by a comparable

increase in peak latencies. The button-press response was made simultaneously with, and sometimes even before, the peaking of the P300 component. This has been reported in other studies, especially where instructions to the subject have emphasized speed over accuracy (30).

We conclude that 50 min after administration of an intravenous dose of midazolam, significant CNS effects are still present and are associated with an increased RT. We have shown that objective electrophysiologic effects are present at this time, as reflected in the late components of the ERP especially the amplitude of P3N3. Subjects, while maintaining accuracy in a button-press task, rated themselves as experiencing a sedative effect at this time, and a state of subclinical sedation may be demonstrable on repeated VAS ratings. The potential for drug interactions in the postsedative period, such as those reported with narcotics and midazolam, may extend beyond currently accepted time limits (5,6). The duration of this "subclinical" midazolam effect in the postsedative period needs to be determined.

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Acute Tolerance to the Hypnotic Effect of Morphine in Rats

Igor Kissin, MD, PhD, Pamela T. Brown, BS, C. Andrew Robinson, PhD,
and Edwin L. Bradley, Jr, PhD

Department of Anesthesiology, University of Alabama School of Medicine, University of Alabama at Birmingham, Birmingham, Alabama

To demonstrate the development of acute tolerance to the hypnotic effects of morphine, loss and recovery of the righting reflex with a constant-rate morphine infusion was studied in rats. In one group of animals, brain and serum concentrations of morphine were detected (radioimmunoassay) at the time of loss of the righting reflex, and in another group, at the time of the reflex recovery. The morphine infusion at a constant rate of $14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ caused a loss of the righting reflex in all animals that was achieved by

2.5 h. However, this level of response could not be maintained, and at 5 h it began to decline. All animals recovered the righting reflex by the ninth hour, despite the continuing morphine infusion. The morphine brain and serum levels at the times of loss and recovery of the righting reflex were not different. The results suggest a development of acute tolerance to the hypnotic effect of morphine, which is determined primarily by pharmacodynamic mechanisms.

(Anesth Analg 1991;73:619-21)

We previously found that during a constant-rate 8-h infusion of morphine, its analgesic effect, after an initial increase, declined profoundly despite the absence of any decrease in morphine brain concentration (1). This indicates the development of acute tolerance, which is pharmacodynamic in nature. Tolerance to opioids does not develop uniformly to all the actions of opioid drugs: there may be complete tolerance to some actions, whereas responses to others are relatively unaltered (2). Hall et al. (3) reported a significant decline in the degree of enflurane MAC (minimum alveolar concentration of the anesthetic that produces immobility to a noxious stimulus) reduction when a stable plasma sufentanil level was maintained for 7 h in dogs. The authors used the degree of MAC reduction as a measure of sufentanil ability to act as an anesthetic. They suggested a development of acute tolerance to the anesthetic effect of sufentanil. Askitopoulon et al. (4) demonstrated an acute tolerance to the inhibitory effect of fentanyl on cardiovascular responses evoked by noxious stimulation in dogs anesthetized with methohexitone. These studies proved that acute tolerance to the antinociceptive effects of opioids can develop in anesthesia. The purpose of the present

study was to demonstrate the development of acute tolerance to the hypnotic effect of morphine.

Methods

Experiments were performed on 20 male Sprague-Dawley rats weighing 225–275 g. The protocol for this study was approved by the Institutional Panel on Laboratory Animal Care of the University of Alabama School of Medicine. The hypnotic effect of morphine was determined with the use of the righting reflex test. Righting reflex test was regarded as positive if the rat failed to right itself (with all four feet on the table) within 15 s after being placed on its back.

A catheter (PE50) for drug infusion was chronically implanted into the jugular vein, and its free end was exteriorized through the skin at the back of the neck. The surgical procedure for implantation was performed under pentobarbital anesthesia (50 mg/kg, intraperitoneally) several days before the experiment. Morphine sulfate was used in the study. The doses of morphine were expressed in terms of the salt. Morphine was infused at a constant rate of $14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ ($0.6 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). The rate was selected (pilot experiments) to provide, first, a loss of the righting reflex and then its recovery in all animals within a 9-h interval. The righting reflex was tested at half-hour intervals during the infusion until all animals lost the righting reflex, then the righting reflex

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Address correspondence to Dr. Kissin, Department of Anesthesiology, University of Alabama School of Medicine, University of Alabama at Birmingham, UAB Station, Birmingham, AL 35294.

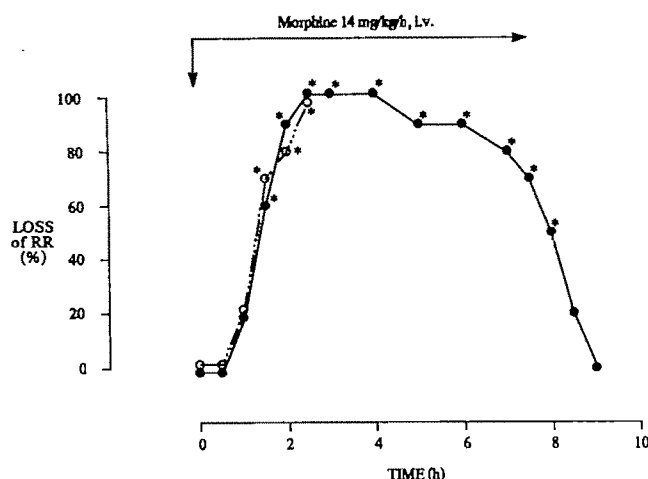


Figure 1. Time-course of the hypnotic effect with morphine infusion at a rate of $14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ as reflected by the frequency of loss of the righting reflex (RR). Solid line, recovery group ($n = 10$); interrupted line, induction group ($n = 10$). * $P < 0.005$ as compared with time 0.

was regularly checked for recovery as indicated in Figure 1.

Two series of experiments were performed with a random allocation of animals. In one series (induction series, 10 animals), brain and serum concentrations of morphine were determined at the time of loss of the righting reflex. Animals were killed by decapitation, and brain and blood samples were taken for determining the morphine concentration by an investigator blinded to the protocol. In another series (recovery series, 10 animals), brain and blood samples were taken at the time of righting reflex recovery.

The blood sample was allowed to clot and was centrifuged, and the serum was refrigerated. The brain was excised, freed of blood vessels and choroid plexus as much as possible, weighed, and also refrigerated. The whole brain was homogenized in 0.1 M sodium phosphate buffer, pH 8.9, at 1 g of brain per 2 mL of buffer. Brain and serum concentrations of morphine were determined using the radioimmunoassay principle (5).

A solid-phase ^{125}I radioimmunoassay method (Coat-A-Count Morphine Kit; Diagnostic Product Corporation, Los Angeles, Calif.) was used. The sensitivity of the Coat-A-Count Morphine assay is 1 ng/mL , with the variability of the assay $\pm 10\%$. The method is highly specific for morphine: 0.03% antibody cross-reactivity with morphine-3-glucuronide and 0.15% with morphine-6-glucuronide.

For calculations, standard curves were prepared by plotting the percent of bound ^{125}I -morphine versus morphine concentration. A best-fit curve for this relationship was obtained with the RIA Data Reduction computer program. Sample concentrations were obtained by interpolating from the standard curve.

In the third series of experiments (eight animals), the effects of the constant-rate ($14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) morphine infusion on arterial CO_2 tension (PaCO_2) and arterial O_2 tension (PaO_2) were studied. This series of experiments included prior preparation of the rats by insertion of a catheter (PE10) through the femoral artery into the aorta, with the peripheral end of the catheter tunneled subcutaneously and exteriorized at the back of the neck. Heparinized saline (100 U/mL) maintained patency of the catheter. Analysis of arterial blood gases was performed before, at 2.5 h (peak of the hypnotic effect), and at the end of morphine infusion. Rat rectal temperature was measured with a rectal thermistor probe and a telethermometer before and during the morphine infusion.

The serum and brain morphine concentrations at the time of loss and at the time of recovery of the righting reflex and data from analysis of blood gases were summarized as the mean \pm SEM. Comparisons of the mean morphine levels at the time of loss and at the time of recovery of the righting reflex were made with a two-sample t -test. The relationship between percent of animals with loss of the righting reflex and time from start of infusion was compared with a χ^2 -test of proportions (6). The relationship between brain morphine levels and recovery time was assessed with linear regression analysis. Comparisons of mean blood gas levels among times from infusion used a repeated-measures analysis of variance. Pairwise tests between any two means were made with Fisher's protected least significant difference test (6). Differences were declared statistically significant if $P < 0.05$.

Results

The time-course of the hypnotic action of morphine with the constant-rate infusion ($14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) is illustrated in Figure 1, which represents the cumulative number of animals with the blocked righting reflex. Morphine infusion at this rate caused a loss of the righting reflex in all animals that was achieved by 2.5 h. However, this level of response could not be maintained, and at 5 h it began to decline. All animals recovered the righting reflex by the ninth hour, despite the continuing morphine infusion.

Table 1 represents brain and serum morphine concentrations at the times of loss and recovery of the righting reflex with the constant-rate morphine infusion. It indicates that at induction of hypnosis and at recovery, the morphine levels were not different. When the brain morphine concentration was plotted against the recovery time (Figure 2), no statistically significant relationship ($r = -0.20$, $P = 0.54$) between these two variables was found.

The constant-rate morphine infusion ($14 \text{ mg} \cdot \text{kg}^{-1}$.

Table 1. Brain and Serum Morphine Concentrations at the Times of Loss and Recovery of the Righting Reflex With the Constant-Rate ($14 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) Morphine Infusion

Group	n	Brain concentration (ng/g)	Serum concentration (ng/mL)
LRR	10	568 ± 62	4195 ± 996
RRR	10	544 ± 37	5443 ± 1296
		NS	NS

LRR, loss of righting reflex; RRR, recovery of righting reflex.
Values are mean \pm SEM.
*As compared with LRR.

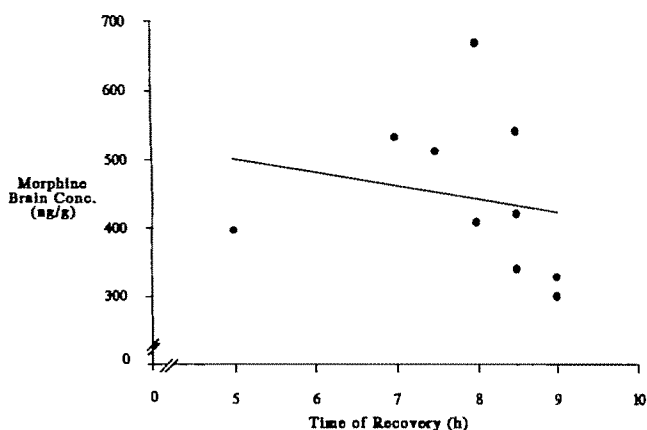


Figure 2. Scatter diagram of morphine brain concentration versus time of righting reflex recovery. Each dot reflects a separate experiment: brain concentration at a time of the recovery. $r = -0.20$, $P = 0.57$.

h^{-1}) caused a decrease in Pao_2 from $89 \pm 4 \text{ mm Hg}$ to $56 \pm 9 \text{ mm Hg}$ at 2.5 h and $64 \pm 4 \text{ mm Hg}$ at the end of infusion. The decrease was statistically significant ($P < 0.01$), although there was only a tendency for the difference between the values at 2.5 h and at the end of infusion. The Paco_2 values changed from $37 \pm 1 \text{ mm Hg}$ to $54 \pm 6 \text{ mm Hg}$ at 2.5 h and $51 \pm 2 \text{ mm Hg}$ at the end of infusion ($P < 0.001$ for the differences from the baseline). The rectal temperature at the end of infusion was $36.7 \pm 0.4^\circ\text{C}$ as compared with $38.2 \pm 0.1^\circ\text{C}$ before infusion ($P < 0.001$).

Discussion

Our experiments demonstrated that during the constant-rate infusion of morphine, the hypnotic effect was not maintained. By 2.5 h after the beginning of

the infusion, the righting reflex was lost in all animals. By the fifth hour, the incidence of the effect began to decline gradually, and by the ninth hour of infusion all animals regained the righting reflex. The changes in arterial blood gases and body temperature during the infusion of morphine were of such magnitude or direction that they could not contribute to the observed decline.

The decline of the effect despite the constant-rate infusion indicates a development of acute tolerance to the hypnotic effect of morphine. Morphine brain concentration at the recovery of the righting reflex during the course of infusion did not decrease compared with that at the loss of the righting reflex at the beginning of the infusion. This suggests that the acute tolerance that developed during morphine infusion does not result from a decrease in brain concentration of the drug. Acute tolerance to the hypnotic effect of morphine is probably determined primarily by pharmacodynamic mechanisms.

Acute tolerance to the sedative effect of morphine has been reported by several authors (7,8). Therefore, the development of acute tolerance to the hypnotic effect of morphine agrees with the above data on the acute tolerance to the morphine sedative effect.

Thus, acute tolerance is demonstrated to both antinociceptive (1,3,4) and hypnotic actions of morphine. Because both actions represent the basis for opioid-induced anesthesia, perhaps acute tolerance plays an important role in anesthesia provided with the use of opioid drugs.

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Comparison of Ocfentanil and Fentanyl as Supplements to General Anesthesia

James E. Fletcher, MB, BS, MRCP, FFARCS, Peter S. Sebel, MB, BS, PhD, FFARCSI,
Michael R. Murphy, MD, Stephan A. Mick, RN, and Seymour Fein, MD

Department of Anesthesiology, Emory University School of Medicine, Atlanta, Georgia, and Anaquest, Milburn, New Jersey

Three doses of ocfentanil (1, 3, and 5 $\mu\text{g/kg}$), a new narcotic, were compared with fentanyl (5 $\mu\text{g/kg}$) as a supplement to general anesthesia. Sixty adult ASA I-III patients undergoing elective surgery were studied. The drugs were given as a bolus injection during induction of anesthesia in a double-blind manner. With the stimulus of tracheal intubation, systolic arterial blood pressure increased (mean \pm SE) from 127 ± 6.9 to 183 ± 7.4 mm Hg and heart rate increased from 82.1 ± 4.8 to 104 ± 6.4 beats/min in patients who had received 1 $\mu\text{g/kg}$ of ocfentanil intravenously. In comparison to patients who received 1 $\mu\text{g/kg}$ of ocfentanil, the increases in heart

rate and systolic arterial blood pressure at the time of tracheal intubation were less with 3 and 5 $\mu\text{g/kg}$ of ocfentanil and 5 $\mu\text{g/kg}$ of fentanyl ($P < 0.05$). At incision, heart rate decreased after the intravenous administration of 5 $\mu\text{g/kg}$ of ocfentanil when compared with patients who received 1 $\mu\text{g/kg}$ of ocfentanil. There were differences between study groups in the mild increase in arterial blood pressure observed at incision. The authors conclude that ocfentanil and fentanyl appear to be similar in action, with 3 $\mu\text{g/kg}$ of ocfentanil being approximately equivalent in effect to 5 $\mu\text{g/kg}$ of fentanyl.

(Anesth Analg 1991;73:622-6)

Ocfentanil (A-3217) is a new opioid with the chemical name of 1-(2-phenylethyl)-4-[N-(2-fluorophenyl)methoxyacetamido] piperidine hydrochloride. It is soluble in aqueous media at a pH below 7 (pKa 7.82) and the solution used for this study had a pH of 5.5. It is stable to moderate heat and light.

Ocfentanil was developed as one of a series of potent naloxone-reversible opioids in an attempt to obtain an opioid that had better therapeutic indices in terms of cardiovascular effects and respiratory depression than fentanyl. If significant improvements were found, then these could be translated into intraoperative and postoperative advantages.

The therapeutic indices were measured by determining the effective dose (in 50% of awake rats) and comparing it to the dose that would cause 50% change in the measured parameter in anesthetized rats (Table 1). Depending on the test used, ocfentanil was three- to eightfold better than fentanyl for hypo-

tension, 3.5- to 8.5-fold better for bradycardia, and three- to sevenfold better for respiratory depression (data on file, Anaquest).

Ocfentanil also appeared to offer pharmacodynamic advances in terms of duration and hypnotic effect. Ocfentanil showed less tendency to accumulate (measured by duration of action) using up to 8 to 16 times ED_{50} compared with fentanyl. Duration of action was comparable to escalating doses of alfentanil (data on file, Anaquest). This profile was deemed desirable in lieu of actual pharmacokinetic data.

Data obtained in rats suggested a three- to fourfold greater separation between hypnotic (loss of righting) and analgesic (tail flick) ED_{50} values for ocfentanil than fentanyl or alfentanil (data in file, Anaquest). This could possibly allow easier titration to either effect.

A study in human volunteers using up to 3 $\mu\text{g/kg}$ showed analgesia and respiratory depression to occur with ocfentanil in a dose-related manner (1). The analgesic effect was maximal at 6 min (using tibial and manubrial algometry) and had largely disappeared 1 h after its administration. Measurements of respiratory rate showed a maximum decrease at 6 min after ocfentanil administration, but the depression persisted for longer than analgesia. Arterial CO_2

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Address correspondence to Dr. Sebel, Department of Anesthesiology, Crawford Long Hospital of Emory University, Glenn Building, 25 Prescott Street NE, Atlanta, GA 30308.

Table 1. Therapeutic Indices for Ocfentanil and Fentanyl in Rats

Analgesic test	Blood pressure (mm Hg)	Heart rate (beats/min)	Respiratory rate (breaths/min)
Tail flick			
Ocfentanil	2.2	6.8	5.5
Fentanyl	0.7	1.9	1.9
Hot plate			
Ocfentanil	1.6	5.2	4.3
Fentanyl	0.2	0.6	0.6

The therapeutic indices are the ratio between the effective dose (in 50% of conscious animals) and the dose that will produce a 50% decrease in mean arterial pressure, a 50% decrease in heart rate, and a 50% increase in end-tidal CO₂ in isoflurane-anesthetized rats.

tension increased to a maximum within 5 min and showed recovery between 60 and 240 min after ocfentanil administration. There was considerable variation in the concentration response relationship after 30 min.

This study was designed to determine the efficacy of ocfentanil and to compare its potency to fentanyl when used as a supplement to general anesthesia.

Methods

After Human Investigation Committee approval had been obtained, 60 ASA physical status I-III patients between 18 and 65 yr of age and scheduled for elective surgery gave written informed consent before participation. Patients were randomly allocated to one of four groups: ocfentanil, 1 µg/kg; ocfentanil, 3 µg/kg; ocfentanil, 5 µg/kg; and fentanyl, 5 µg/kg. Ocfentanil (1 µg/kg) was chosen as it has been shown that this dose caused effective analgesia in volunteers (1). Ocfentanil (3 µg/kg) produced a greater analgesic effect with associated respiratory depression (1). Patients were premedicated with 5-10 mg of diazepam orally 1 h before operation and with 10 mg of metoprolol and 150 mg of ranitidine orally 2 h before operation.

Lactated Ringer's solution was infused and standard monitoring techniques (i.e., automated blood pressure cuff [Dinamap], electrocardiogram, pulse oximeter, and precordial stethoscope) were used. The test drug solution (ocfentanil or fentanyl) was administered intravenously in a double-blind fashion 1 min before induction of anesthesia with 2 mg/kg of thiopental over 30 s followed by 50 mg every 15 s until the lash reflex was abolished. Neuromuscular block was accomplished with 0.1 mg/kg of vecuronium before tracheal intubation, after which mechanical ventilation with oxygen (33%) and nitrous oxide (67%) was begun. End-tidal CO₂ tension was maintained between 30 and 35 mm Hg.

Hemodynamic variables were recorded every minute for the first 20 min after anesthetic induction, for the first 5 min after surgical incision, and every 5 min thereafter. Isoflurane was administered when heart rate or arterial blood pressure increased to more than 20% above preinduction values after the initial cardiovascular effects of tracheal intubation had subsided.

Statistical analysis included repeated measures analysis of variance with Bonferroni *t*-test and Student's *t*-test as appropriate. Statistical significance was taken as *P* < 0.05. Results are expressed as the mean ± SE.

Results

Sixty patients were divided into four groups of 15 each. There were no significant differences among any of the groups with respect to weight (75.8 ± 1.9 kg). The group receiving 1 µg/kg of ocfentanil (age, 49.4 ± 3.6 yr) was significantly older than the group receiving 3 µg/kg of ocfentanil (age, 39.3 ± 3.2 yr). There were no statistically significant differences in the thiopental anesthetic induction doses (milligrams per kilogram) or in the times to initiating isoflurane administration among any of the groups (Table 2).

At the time of tracheal intubation, the magnitude of changes in heart rate and arterial blood pressure were inversely related to the dose of ocfentanil. There were significant differences between groups (*F* = 12.62, *P* < 0.01) and with time (*F* = 37.79, *P* < 0.01) for systolic blood pressure, and between groups (*F* = 4.58, *P* < 0.01) and with time (*F* = 31.34, *P* < 0.01) for heart rate. Ocfentanil (1 µg/kg) was associated with a higher systolic blood pressure immediately before laryngoscopy and throughout the first 5 min after tracheal intubation compared with the other doses of ocfentanil and fentanyl. The 1 µg/kg dose of ocfentanil was also associated with a higher heart rate than the 5 µg/kg dose (Figures 1 and 2).

At the time of skin incision, changes in heart rate and arterial blood pressure were less than those after tracheal intubation. Differences in heart rate were evident between the groups (*F* = 3.73, *P* < 0.02), although not with time (*F* = 0.24, *P* < 0.95). The 5 µg/kg dose of ocfentanil was associated with a lower heart rate than the 1 µg/kg dose. Although systolic blood pressure showed a difference over time (*F* = 12.9, *P* < 0.01), there were no differences between groups (*F* = 0.68, *P* < 0.58) (Figures 3 and 4).

Discussion

Opioid analgesics reduce anesthetic requirements and blunt the cardiovascular response to tracheal in-

Table 2. Effect of Ocfentanil and Fentanyl on Anesthetic Requirements

	Ocfentanil (1 $\mu\text{g/kg}$)	Ocfentanil (3 $\mu\text{g/kg}$)	Ocfentanil (5 $\mu\text{g/kg}$)	Fentanyl (5 $\mu\text{g/kg}$)
Thiopental dose (mg/kg)	3.2 ± 0.34	2.9 ± 0.21	2.6 ± 0.21	3.0 ± 0.20
Time to beginning isoflurane administration (min)	19.5 ± 8.1	27.5 ± 6.1	29.3 ± 4.9	20.7 ± 5.4

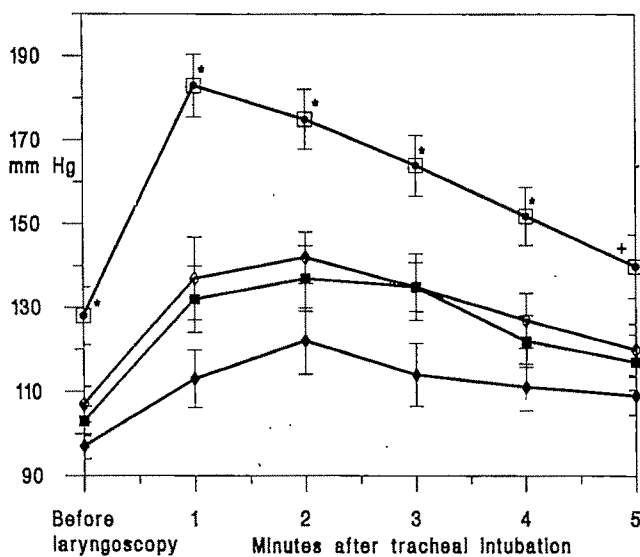
Data are mean \pm SE.

Figure 1. Systolic arterial blood pressure just before laryngoscopy and in the first 5 min after tracheal intubation with three different doses of ocfentanil and one dose of fentanyl. Data are mean \pm SE. * $P < 0.05$ compared with all other groups. † $P < 0.05$ compared with 5 $\mu\text{g/kg}$ of ocfentanil. □, 1 $\mu\text{g/kg}$ of ocfentanil; ■, 3 $\mu\text{g/kg}$ of ocfentanil; ◆, 5 $\mu\text{g/kg}$ of ocfentanil; ◇, 5 $\mu\text{g/kg}$ of fentanyl.

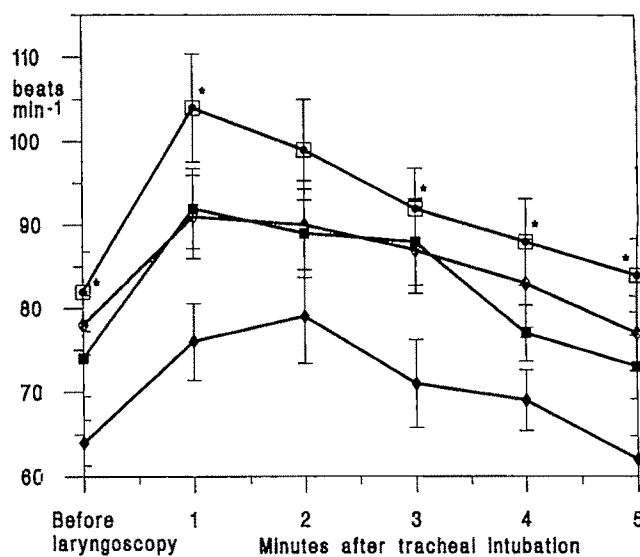


Figure 2. Heart rate just before laryngoscopy and in the first 5 min after tracheal intubation with three different doses of ocfentanil and one dose of fentanyl. Data are mean \pm SE. * $P < 0.05$ compared with 5 $\mu\text{g/kg}$ of ocfentanil. □, 1 $\mu\text{g/kg}$ of ocfentanil; ■, 3 $\mu\text{g/kg}$ of ocfentanil; ◆, 5 $\mu\text{g/kg}$ of ocfentanil; ◇, 5 $\mu\text{g/kg}$ of fentanyl.

tubation and skin incision (2). In animals, ocfentanil has the properties of an opioid drug (data on file, Anaquest). It is, however, difficult to extrapolate data obtained from animals to humans as species differences exist in both the sensitivity (3) and pharmacodynamic effects (4) of opioids. Furthermore, the methods of assessing analgesia are not the same in animals and humans. Commonly used methods of directly assessing analgesia in animals are with the hot plate and tail flick responses in rats (5). Direct methods in humans include dolorimetry (6-8), tourniquet ischemia time (9), and tibial (1,8) and manubrial (1) algometry. Placebo responses, which do not occur in animal experiments, complicate these human experiments. It is therefore more difficult to measure analgesic efficacy in humans by these direct methods. Indirect methods of determining analgesic efficacy and potency in humans (i.e., bypassing the subjective description of pain and investigating a physiologically mediated, pain-induced response) include the effect of the analgesics on the minimum

alveolar concentration of volatile anesthetics that will suppress movement to noxious stimulation and the interaction of analgesics with the cardiovascular responses to noxious stimuli.

Administering fentanyl before induction of anesthesia allows a smaller dose of thiopental to be used to achieve loss of consciousness (10,11). In one study, administering 5 $\mu\text{g/kg}$ of fentanyl 3 min before induction of anesthesia resulted in loss of consciousness after 1.7 ± 0.33 mg/kg of thiopental had been given (10). In our study, when induction of anesthesia began 1 min after giving 5 $\mu\text{g/kg}$ of fentanyl, a thiopental dose of 3.0 ± 0.20 mg/kg was required for loss of consciousness. This difference is probably explained by the shorter interval between administering fentanyl and thiopental. Also, the size of the incremental doses of thiopental and the time intervals between them (25 mg every 30 s in the study by Bowdle and Ward [10] and 50 mg every 15 s in our study) may contribute to the differences in thiopental requirements. Although our study suggested a dose-related reduction in thiopental requirements with

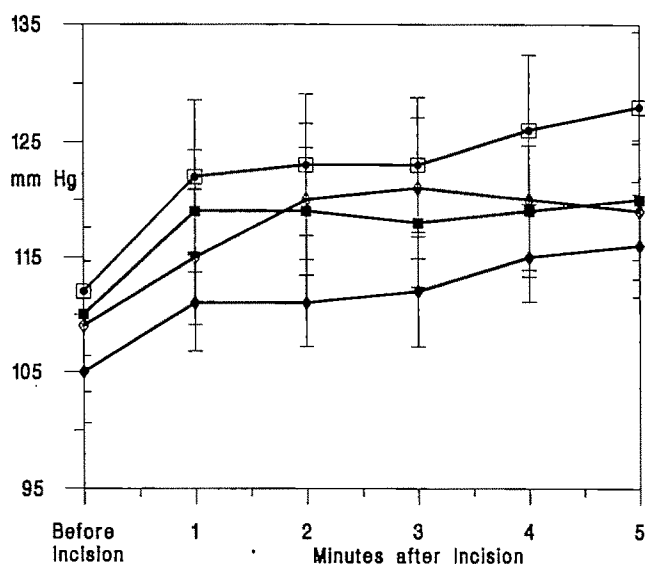


Figure 3. Systolic arterial blood pressure just before skin incision and in the first 5 min after incision with three different doses of ocfentanil and one dose of fentanyl. Data are mean \pm SE. \square , 1 μ g/kg of ocfentanil; \blacksquare , 3 μ g/kg of ocfentanil; \blacklozenge , 5 μ g/kg of ocfentanil; \diamond , 5 μ g/kg of fentanyl.

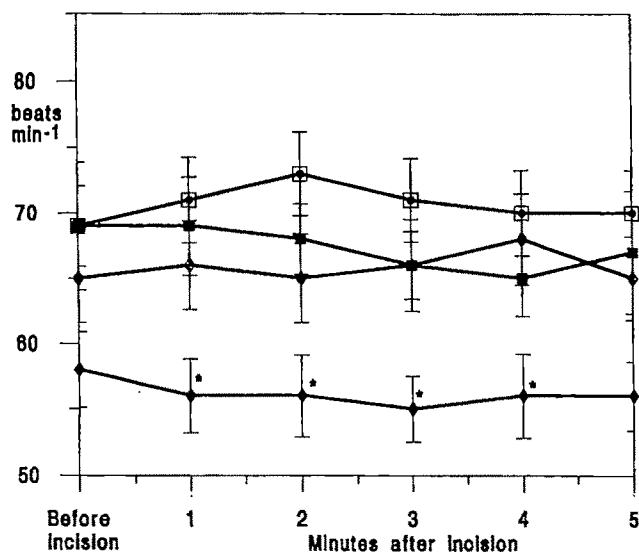


Figure 4. Heart rate just before skin incision and in the first 5 min after incision with three different doses of ocfentanil and one dose of fentanyl. Data are mean \pm SE. * P < 0.05 compared with 1 μ g/kg of ocfentanil. \square , 1 μ g/kg of ocfentanil; \blacksquare , 3 μ g/kg of ocfentanil; \blacklozenge , 5 μ g/kg of ocfentanil; \diamond , 5 μ g/kg of fentanyl.

ocfentanil, the differences were not statistically significant. It is not possible to draw any conclusions therefore about the potency of ocfentanil in relation to fentanyl from our study.

The hemodynamic responses to tracheal intubation are reduced by opioids given in doses comparable to those used in our study (10,12). In another study, control of heart rate responses to laryngoscopy

and tracheal intubation required a considerably higher dose of fentanyl than we used (13). In regard to obtundation of the cardiovascular effects of laryngoscopy and tracheal intubation, the effects of 3 μ g/kg of ocfentanil appeared similar to those of 5 μ g/kg of fentanyl (Figures 1 and 2). One microgram per kilogram of ocfentanil represents an inadequate dose in terms of hemodynamic responses to laryngoscopy as the mean systolic blood pressure increased to greater than 170 mm Hg.

By the time of skin incision, our patients were under more stable conditions of anesthesia, including isoflurane. Thus, it is difficult to make direct comparisons between fentanyl and ocfentanil under these conditions. Heart rate was lower with 5 μ g/kg of ocfentanil than with 1 μ g/kg of ocfentanil, demonstrating the increased duration and efficacy of the increased dose.

To assess opioid efficacy in this study, we used the dose requirement of thiopental, the time to starting isoflurane, and hemodynamic responses as our measures of efficacy. Using similar methodology with another opioid, pentamorphine, we were able to demonstrate clear dose-response relationships for thiopental and isoflurane requirements (14). In this study, we were unable to do so, and the reasons for this are unclear. A 5 μ g/kg dose of ocfentanil is better than a 1 μ g/kg dose at suppressing hemodynamic responses, yet it did not reduce the thiopental requirement. The onset of analgesia with ocfentanil may be slower than with pentamorphine (or fentanyl) and if we had waited longer before administering thiopental, a significant relationship may have been demonstrated.

From this study it is impossible to determine an exact potency relationship between ocfentanil and fentanyl. We have demonstrated that 1 μ g/kg of ocfentanil is an inadequate dose to suppress hemodynamic responses to tracheal intubation. A 3 μ g/kg dose of ocfentanil represents approximate pharmacodynamic equivalency with 5 μ g/kg of fentanyl. In this study, we were unable to demonstrate any obvious advantage of ocfentanil over fentanyl.

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Visual Assessment of Train-of-Four and Double Burst-Induced Fade at Submaximal Stimulating Currents

Sorin J. Brull, MD, and David G. Silverman, MD

Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut

The influence of current intensity on visual assessment of fade in response to train-of-four (TOF) and two modes of double-burst stimulation (DBS) was determined to assess the utility of low-current neurostimulation. Each of 150 sets of assessments (in 51 patients) included a mechanographic TOF at 60 mA followed by visual assessments of TOF, DBS_{3,3} (two minitetic bursts of three stimuli each), and DBS_{3,2} (a burst of three followed by a burst of two impulses) at 20, 30, 50, and 60 mA in random order. For the range of mechanographic TOF ratios between 0.41 and 0.70, visual assessment of TOF fade failed to identify fade in 33%, 36%, 44%, and 58% of cases at 20, 30, 50, and 60 mA, respectively. Corresponding false-negative rates for DBS_{3,3} were 11%, 17%, 36%,

and 33%, and for DBS_{3,2} they were 6%, 6%, 17%, and 28%. Within each method, $P < 0.05$ (by Mantel-Haenszel analysis) for a linear trend of increasing accuracy as current decreased. For the range between 0.41 and 0.70, quantitative assessment overestimated the actual ratio at all currents for TOF, at 30, 50, and 60 mA for DBS_{3,3}, and at 50 and 60 mA for DBS_{3,2} ($P < 0.05$ by Wilcoxon signed rank test). At each current tested, DBS was more sensitive in detecting fade visually than TOF. The accuracy of visual fade detection was not influenced significantly by level of observer training. In conclusion, visual assessment of fade by novice and expert observers is improved by testing at low currents.

(Anesth Analg 1991;73:627-32)

Mechanographic assessment of the response to train-of-four (TOF) stimulation is used to determine magnitude of neuromuscular blockade. In clinical practice, however, anesthesiologists often rely on visual assessment of response to TOF. One limitation is that such assessment often misses significant degrees of fade (1-6). This limitation partially has been overcome by the increased sensitivity afforded by double-burst stimulation (DBS) (7-9).

Testing with submaximal stimulating currents may be preferable, primarily because they are associated with less discomfort than supramaximal currents (10). The consistency of mechanographic TOF and DBS fade has been documented over a wide range of stimulating currents (11,12). The present study was undertaken to define the accuracy of visual assessment of TOF- and DBS-induced fade at stimulating currents of 20, 30, 50, and 60 mA. For reasons of completeness and because both modes are used

clinically, DBS_{3,3} (a minitetic burst consisting of three impulses, followed 750 ms later by an identical burst) and DBS_{3,2} (for which the second burst consisted of only two impulses) were evaluated in the present study. In addition to the qualitative assessment as to presence or absence of fade, observers also quantified the degree of such fade. This provided a better appreciation of the shortcomings of nonmechanographic assessment of neuromuscular fade.

Methods

Before initiating the clinical study, the outputs of a DualStim Plus (Professional Instruments, Houston, Tex.) and a Myotest nerve stimulator (Biometer, Copenhagen, Denmark) were tested with an interfaced oscilloscope to confirm consistency of current output at varying resistances and accuracy of dial settings.

After institutional investigational review board approval had been obtained, data were collected on 51 consenting ASA physical status I-III patients undergoing general endotracheal anesthesia. Patients ranged in age from 18 to 80 yr, were within 50% of their ideal body weight, and were free of known

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Address correspondence to Dr. Brull, Yale University School of Medicine, Department of Anesthesiology, 333 Cedar Street, New Haven, CT 06510.

neuromuscular disease. For all neuromuscular monitoring, the ulnar nerve was stimulated via cutaneous electrodes ("Huggables" Infant Monitoring Electrode, Medtronic/AMI, Haverhill, Mass.) placed with the positive electrode over the olecranon groove and the negative electrode on the distal volar forearm. Train-of-four stimulation with square-wave impulses of 200- μ s duration was provided by a DualStim Plus. DBS_{3,3} and DBS_{3,2} stimulation with square-wave impulses of 200- μ s duration at 50 Hz were delivered by a Myotest nerve stimulator. Thumb adduction in response to all neurostimulation was quantified with an adductor pollicis force transducer that was interfaced to a monitor/strip chart recorder.

Anesthesia was induced with 3-6 mg/kg of thiopental, 1-2 μ g/kg of fentanyl, and 0.01-0.04 mg/kg of midazolam administered intravenously. Tracheal intubation was facilitated with intravenous succinylcholine (1-1.5 mg/kg), and anesthesia was maintained with 0.25%-1.25% end-tidal isoflurane and 66% nitrous oxide in oxygen. After return of neuromuscular function was documented, 0.5-1.5 mg of vecuronium was administered intravenously. A continuous infusion of vecuronium (0.1-1.5 μ g·kg⁻¹·min⁻¹) was started to achieve a stable degree of neuromuscular blockade. Once the TOF ratio varied by less than 10% over a 10-min period, a mechanographic recording of the TOF was obtained at supramaximal (60-70 mA) current (and was repeated at the end of the testing sequence) to ensure consistency of the depth of blockade. The thumb then was removed from the ring of the adductor pollicis force transducer and an observer, blinded to the presence or degree of neuromuscular blockade, was asked to evaluate visually the presence of fade in response to TOF, DBS_{3,3}, and DBS_{3,2}. The 150 observers participating in the evaluation were medical students, anesthesia residents, and faculty. None of the observers participated in evaluation of the same patient more than once. In addition to qualitative assessments, if the observer reported presence of fade, then he or she was asked to estimate the TOF and DBS ratios to the nearest 5%. For each method of neurostimulation (TOF, DBS_{3,3}, and DBS_{3,2}), each observer was asked to evaluate responses to currents of 20, 30, 50, and 60 mA. These currents were obtained by adjusting the stimulator's calibrated rheostat. The 12 determinations were performed by each observer at 20-s intervals in random sequence in the presence of one of the investigators (S.J.B.), such that a total of 1800 assessments were recorded.

Each of the 150 sets of assessments was assigned to one of four subgroups based on the mechanographic TOF ratio: 0.06-0.40, 0.41-0.70, 0.71-0.90, and 0.91-1.0. The ability to predict by visual assessment whether the mechanographic TOF ratio was above or below 0.70 (i.e., *qualitative* assessment) was deter-

mined at each current for TOF, DBS_{3,3}, and DBS_{3,2} in each of the four subgroups. Intercurrent and intertechnique comparisons were performed with χ^2 analysis and, for each technique, intercurrent trends were assessed by Mantel-Haenszel analysis.

The ability to assess the TOF ratio *quantitatively* by visual inspection likewise was determined for each current of each technique. Within each of the four subgroups, the differences between the estimated and the actual mechanographic ratios at each current were analyzed by Wilcoxon signed rank test. Differences were considered statistically significant at the $P < 0.05$ level for all analyses.

In addition, at the extremes of current (i.e., 20 and 60 mA), scattergrams were generated to delineate the relationship between visual assessment and the actual mechanographic TOF ratio. For each of the 150 sets of assessments of a given technique at a given current, the accuracy of fade assessment was delineated by dividing each scattergram into four quadrants:

- I. Failure to detect mechanographic ratio < 0.70 (false negative)
- II. Correct identification of TOF ≥ 0.70 (true negative)
- III. Correct identification of TOF < 0.70 (true positive)
- IV. Incorrect assessment of TOF ≥ 0.70 (false positive)

To delineate the influence of assessors' experience on the accuracy of fade detection, data also were grouped according to the assessors' level of training; the "novice" group ($n = 79$) included medical students, interns, and residents in their first or second year of clinical anesthesia training. The "expert" group ($n = 71$) included residents in their third and fourth year of training and anesthesia attendings, all of whom had used nerve stimulators in their daily practice for at least 3 yr. Differences in the ability to identify fade were analyzed by χ^2 test.

Results

There was a high incidence of failure to detect fade by visual assessment in the critical range of mechanographic ratios between 0.41 and 0.70 (Figure 1). For each technique, there was a significant linear trend between stimulating current and incidence of false-negative assessments. In the three remaining subgroups, there were no significant intertechnique or intercurrent differences with respect to the ability to visually categorize TOF and DBS ratios as either more than or less than 0.70. Among the techniques, the sensitivity of DBS_{3,2} to detect fade was greater than

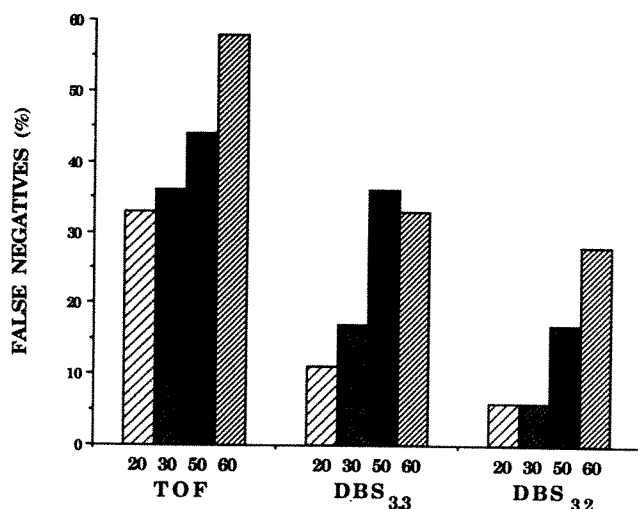


Figure 1. Failure to detect fade when the mechanographic train-of-four ratio is between 0.41 and 0.70 for the three techniques at each of four stimulating currents. For each technique, there was a direct linear relationship between current intensity and false-negative rates. Significant intercurrent differences were noted for 20 vs 50 mA and for 20 vs 60 mA of DBS_{3,3} and for 20 vs 60 mA and for 30 vs 60 mA of DBS_{3,2}.

that of TOF at all currents tested ($P < 0.05$); there were no differences in the sensitivities among the two DBS techniques at any of the stimulating currents ($P = \text{NS}$).

Figure 2 illustrates the overestimation of the actual ratio when assessed visually, especially at higher stimulating currents. The degree of overestimation within the four subgroups is detailed in Table 1. It was most pronounced with TOF at high currents and least evident with DBS_{3,2}.

The individual relationships between the visual estimation of the degree of fade and the actual mechanographic TOF ratio are illustrated in Figures

3-5. For TOF, mechanographic values as low as 0.10 and 0.14 were estimated to be more than 0.70 by visual assessment at 20 and 60 mA, respectively. For DBS_{3,3}, mechanographic values as low as 0.08 and 0.14 were estimated to be more than 0.70 by visual assessment at 20 and 60 mA, respectively. For DBS_{3,2}, mechanographic values as low as 0.08 and 0.10 were estimated to be more than 0.70 by visual assessment at 20 and 60 mA, respectively.

There were no significant differences in the ability of novice ($n = 948$) and expert ($n = 852$) assessors to correctly predict the TOF ratio by visual means (Figures 3-5; Table 2).

Discussion

The present study documents that the ability to detect fade by visual inspection is not compromised by assessment performed with low stimulating currents. Qualitatively, there actually was a significant inverse linear relationship between stimulating current and ability to identify fade. Quantitatively, the degree of overestimation of the actual ratio was less when estimates were based on assessment at low current. As did other investigators (7,8), we found that DBS-induced fade was detected more reliably than that induced by TOF. DBS_{3,2} was the most sensitive, but it also was associated with a relatively high incidence of falsely suggesting fade even when the mechanographic TOF ratio was more than 0.90. This is attributable to the artificially induced "fade" of DBS_{3,2} as a result of the shorter duration of the second burst.

Yet, visual assessment at any current is not necessarily a reliable substitute for mechanographic measurements. Consistent with previous investigations (1,6-8), visual assessment at 60 mA failed to identify

Figure 2. Comparison of visual estimates of fade to the mechanographic (actual) ratio for data sets with mechanographic ratios < 0.70 . Quantitative estimations by visual means significantly overestimated the actual ratio (shown as the unshaded bar) at all currents for train-of-four, at currents of 30, 50, and 60 mA for DBS_{3,3}, and at 50 and 60 mA for DBS_{3,2}.

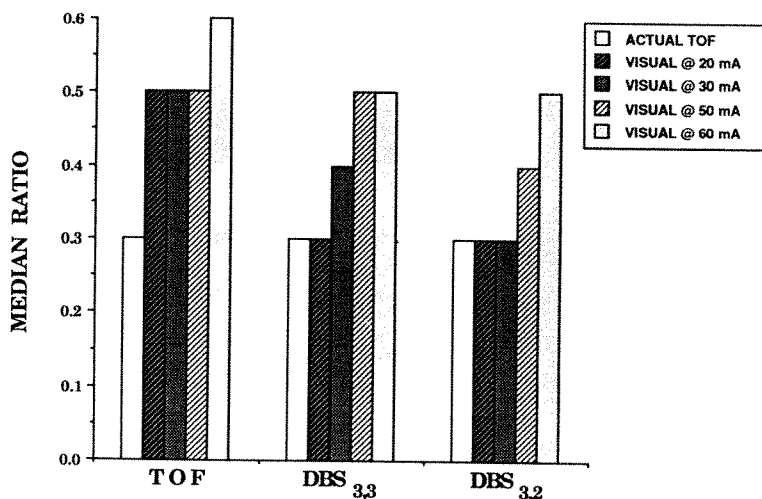


Table 1. Visual Estimation of Ratio

	Actual TOF ratio	Visual estimation of TOF				Visual estimation of DBS _{3,2}				Visual estimation of DBS _{3,2}			
		20 mA	30 mA	50 mA	60 mA	20 mA	30 mA	50 mA	60 mA	20 mA	30 mA	50 mA	60 mA
Subgroup I													
Median	0.2	0.4 ^a	0.4 ^a	0.5 ^a	0.5 ^a	0.5 ^a	0.3 ^a	0.4 ^a	0.5 ^a	0.2 ^b	0.2 ^a	0.3 ^a	0.4 ^a
Range	0.06-0.40	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-0.8	0.1-1.0
Mean \pm SD	0.2 \pm 0.1	0.4 \pm 0.3	0.4 \pm 0.2	0.5 \pm 0.2	0.5 \pm 0.2	0.6 \pm 0.2	0.3 \pm 0.3	0.4 \pm 0.2	0.5 \pm 0.2	0.3 \pm 0.3	0.3 \pm 0.2	0.4 \pm 0.2	0.4 \pm 0.2
Subgroup II													
Median	0.6	0.8 ^a	0.9 ^a	0.9 ^a	1.0 ^a	1.0 ^a	0.5	0.8 ^a	0.8 ^a	0.5	0.6	0.6 ^a	0.8 ^a
Range	0.41-0.70	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.2-1.0	0.4-1.0	0.1-1.0	0.1-1.0	0.2-1.0	0.2-1.0
Mean \pm SD	0.6 \pm 0.1	0.7 \pm 0.3	0.8 \pm 0.2	0.8 \pm 0.3	0.8 \pm 0.3	0.8 \pm 0.3	0.6 \pm 0.3	0.7 \pm 0.2	0.8 \pm 0.2	0.6 \pm 0.2	0.6 \pm 0.2	0.7 \pm 0.2	0.7 \pm 0.3
Subgroup III													
Median	0.8	1.0 ^a	1.0 ^a	1.0 ^a	1.0 ^a	1.0 ^a	0.9	1.0 ^a	1.0 ^a	0.9	0.8	0.8	0.8
Range	0.71-0.90	0.4-1.0	0.5-1.0	0.8-1.0	0.8-1.0	0.6-1.0	0.5-1.0	0.6-1.0	0.6-1.0	0.1-1.0	0.1-1.0	0.1-1.0	0.4-1.0
Mean \pm SD	0.8 \pm 0.05	0.9 \pm 0.2	0.9 \pm 0.1	1.0 \pm 0.1	1.0 \pm 0.1	1.0 \pm 0.1	0.8 \pm 0.2	0.9 \pm 0.1	0.9 \pm 0.1	0.8 \pm 0.2	0.7 \pm 0.2	0.7 \pm 0.2	0.8 \pm 0.2
Subgroup IV													
Median	1.0	1.0 ^a	1.0	1.0 ^a	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0 ^a	1.0
Range	0.91-1.0	1.0-1.0	1.0-1.0	1.0-1.0	1.0-1.0	0.7-1.0	0.8-1.0	0.9-1.0	0.8-1.0	0.5-1.0	0.6-1.0	0.5-1.0	0.3-1.0
Mean \pm SD	1.0 \pm 0.03	1.0 \pm 0	1.0 \pm 0.1	1.0 \pm 0	1.0 \pm 0.1	1.0 \pm 0.1	1.0 \pm 0.1	1.0 \pm 0.03	1.0 \pm 0.1	0.9 \pm 0.2	0.9 \pm 0.1	0.9 \pm 0.2	0.9 \pm 0.2

TOF, train-of-four; DBS_{3,2}, double-burst stimulation with three impulses which are repeated after 750 ms; DBS_{3,2}, double-burst stimulation with three impulses which are followed by two impulses after 750 ms.

^aSignificant overestimation of actual (mechanographic) ratio, i.e., significant underestimation of fade.

^bSignificant underestimation of actual (mechanographic) ratio, i.e., significant overestimation of fade.

^cBorderline significance, with $P = 0.054$.

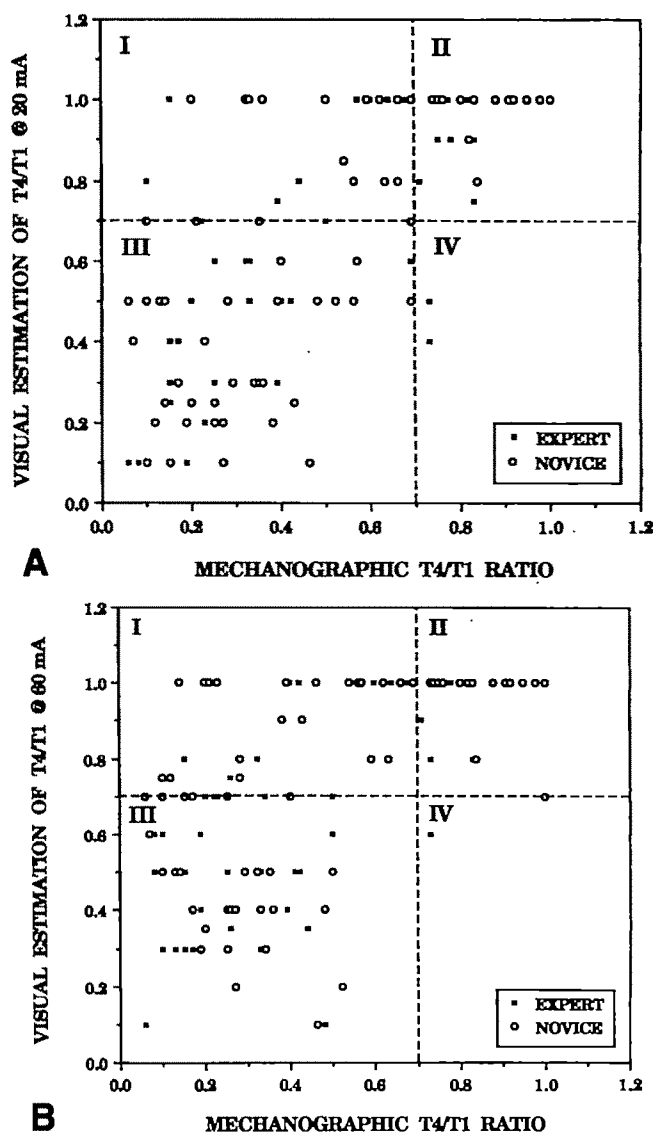


Figure 3. Scattergrams of visual estimations of the T4/T1 ratio vs mechanographic T4/T1. (A) Visual estimation at 20 mA; (B) visual estimation at 60 mA. The four quadrants represent false negatives (I), true negatives (II), true positives (III), and false positives (IV).

fade when the mechanographic ratio was between 0.41 and 0.70 in 58% of cases for TOF, 33% of cases for DBS_{3,2}, and 28% of cases for DBS_{3,2}. Corresponding false-negative rates at 20 mA were 33%, 11%, and 6%. In view of reports that mechanographic TOF and DBS ratios maintain consistency at varying currents (11,12), it is the perception (as opposed to the degree) of fade that is affected by low current. Perhaps small differences may not be appreciated so readily among the more vigorous responses elicited by high current. Regardless of the means of stimulation or the intensity of stimulating current, response to neurostimulation should be viewed in the context of clinical

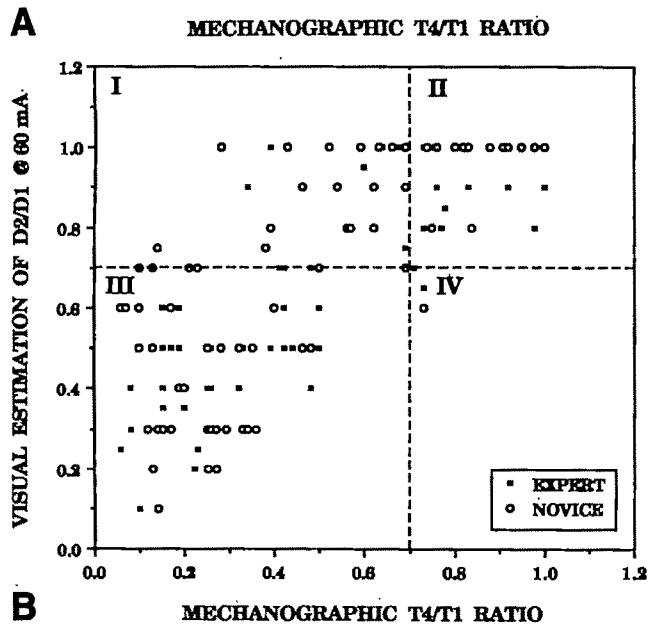
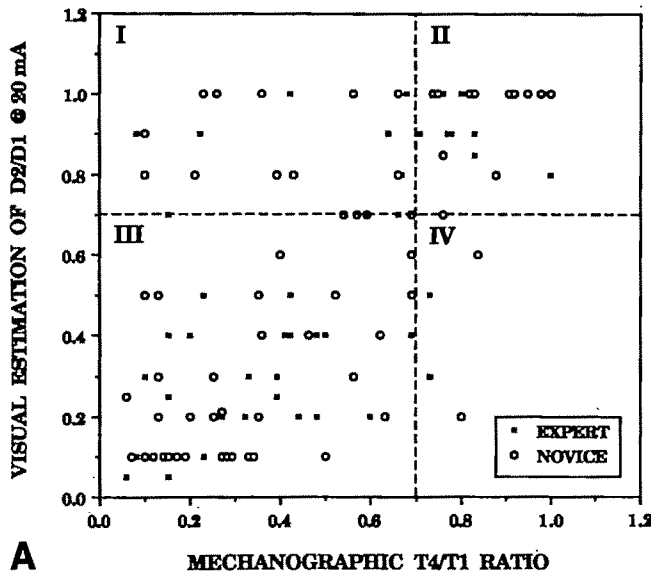


Figure 4. Scattergrams of visual estimations of the $DBS_{3,3}$ D2/D1 ratio vs mechanographic T4/T1. (A) Visual estimation at 20 mA; (B) visual estimation at 60 mA.

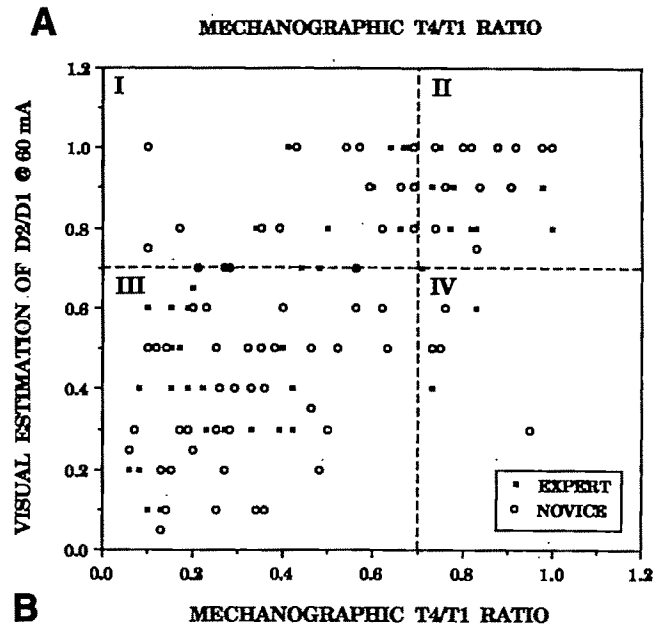
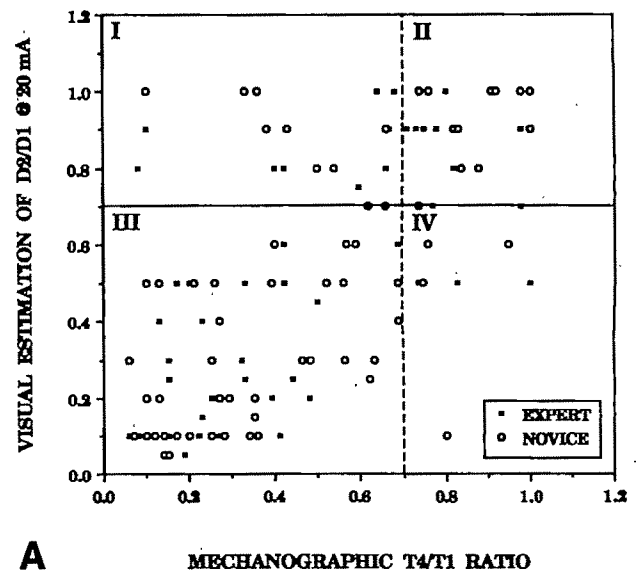


Figure 5. Scattergrams of visual estimations of the $DBS_{3,2}$ D2/D1 ratios vs mechanographic T4/T1. (A) Visual estimation at 20 mA; (B) visual estimation at 60 mA.

Table 2. Sensitivity (%) of Visual Assessment to Train-of-Four Ratio < 0.70

	TOF				$DBS_{3,3}$				$DBS_{3,2}$			
	20 mA	30 mA	50 mA	60 mA	20 mA	30 mA	50 mA	60 mA	20 mA	30 mA	50 mA	60 mA
Actual ratio												
0.06-0.40												
Expert	97	100	100	94	100	100	100	100	100	97	100	97
Novice	90	90	93	88	93	95	100	98	95	95	98	98
Actual ratio												
0.41-0.70												
Expert	65	76	65	47	88	100	82	65	88	88	76	71
Novice	68	53	47	37	100	89	84	80	89	80	53	63

TOF, train-of-four; $DBS_{3,3}$, double-burst stimulation with three impulses which are repeated after 750 ms; $DBS_{3,2}$, double-burst stimulation with three impulses which are followed by two impulses after 750 ms.

Ability to identify fade according to assessor's experience: expert group consists of assessors with ≥ 3 yr experience, novice group consists of assessors with < 3 yr experience in clinical anesthesia.

criteria whenever feasible. The range of blockade between 0.71 and 0.90 posed an interesting problem in that it represents mechanographic TOF fade that may or may not be clinically significant. Although few would argue that a TOF ratio less than 0.70 constitutes significant fade, debate exists as to whether a TOF ratio more than 0.70 necessarily indicates adequate neuromuscular function (13). Hence, a "false" reporting of presence of fade when the mechanographic TOF is more than 0.70 (as tends to occur with DBS_{3,2}) does not necessarily represent a clinical shortcoming.

In conclusion, the use of low current may be preferable when neurostimulation is employed to evaluate neuromuscular blockade. In addition to causing less discomfort, low current does not compromise and actually may improve visual detection of fade regardless of the assessor's level of training. However, the caveat remains that visual assessment is not necessarily a reliable indicator of mechanographic fade.

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Adrenergic Modulation of Preoperative Anxiety: A Comparison of Temazepam, Clonidine, and Timolol

U. A. Carabine, MB, K. R. Milligan, MD, and J. A. Moore, PhD

Department of Anaesthetics, The Queen's University of Belfast and Musgrave Park Hospital, Belfast, Northern Ireland

To assess the influence of adrenergic modulation on preoperative anxiety, we used a randomized, double-blind, placebo-controlled trial to compare temazepam, clonidine, and timolol as preanesthetic medications in patients undergoing minor orthopedic surgery. All the active treatments resulted in less preoperative anxiety than the placebo (control) did. Induction of anesthesia was smoother in all the treated patients compared with the control group. Recovery was slowest in the

temazepam and clonidine groups, but there were no significant differences between the groups after 90 min. Cardiovascular changes were most marked in the timolol group. Pain scores were lower in the temazepam and clonidine series in the early postoperative period. Neither clonidine nor timolol offers any major advantage over temazepam for premedication in these patients.

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Preoperative sedation and anxiolysis are often the main objectives of premedication (1), and both involve a number of possible mechanisms of action including depression of the reticular activating system and activation of the inhibitory neurotransmitter γ -aminobutyric acid. More recent evidence has also implicated central adrenergic receptors (2). Benzodiazepines act predominantly on the limbic system by activation of γ -aminobutyric acid receptors, resulting in anxiolysis and sedation (3) with minimal systemic effects. β -Adrenergic blockers produce marked anxiolysis in the absence of sedation and may be of benefit in ambulatory anesthesia (4). The site of action of β -adrenergic blockers is unclear but is thought to be the reticular activating system, although the reduction in anxiety may be due to peripheral blockade of sympathetically mediated symptoms such as palpitations. This interrupts a feedback loop that could otherwise perpetuate the anxiety (5). α_2 -Adrenergic agonists have sedative, anxiolytic, and analgesic properties (6). Their site of action is probably the locus coeruleus, although α_2 -receptors have been identified in a number of sites within the central nervous system (7). α -Adrenergic agonists, β -adrenergic blockers, and occasionally, benzodiazepines, have significant cardiovascular effects, but previous studies have demonstrated

that these effects are dose-dependent (8-10) and may not preclude their use for premedication.

The aim of this study was to assess and compare the three drug groups for their anxiolytic and sedative properties and for their effect on the induction, maintenance, and recovery from a standard general anesthetic.

The recovery from anesthesia was assessed by the time to recovery, critical flicker frequency (CFF) (11) (an index of cortical activity), and the Treiger test (12) (an indicator of depression of the central nervous system).

Methods

After ethical committee approval and informed patients' consent had been obtained, fit and healthy patients (ASA grade I and II) scheduled for minor orthopedic surgery (arthroscopy) under general anesthesia were included in the study. Patients currently receiving medication or outside the weight range of 50-100 kg were excluded.

During a preoperative visit, arterial blood pressure and heart rate were recorded. The visual analogue scoring system (VAS) was explained to the patients, and a baseline reading for anxiety was recorded using a 100-mm scale with completely calm at one extreme and worst possible anxiety at the other. Critical flicker frequency readings were obtained, and a Treiger test was performed.

Premedication was administered orally 60-90 min preoperatively in a double-blind, randomized fashion

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Address correspondence to Dr. Carabine, Department of Anaesthetics, Whitla Medical Building, 97, Lisburn Road, Belfast, Northern Ireland.

and consisted of either 20 mg of temazepam, 0.2 mg of clonidine, 10 mg of timolol, or a placebo. No other drugs were administered preoperatively. On the patient's arrival in the anesthesia room, sedation was assessed by a blinded observer on a three point scale: awake, drowsy, or asleep. A second VAS for anxiety was completed by the patient. Heart rate, arterial blood pressure, and tissue oxygen saturation monitoring were begun using the Hewlett Packard 78354A system, with a continuous printout available. Anesthesia was induced intravenously with 2 mg/kg of propofol, with increments of 0.5 mg/kg at 10-s intervals until the patient lost response to verbal command. The induction of anesthesia was graded on a four-point scale: 1, smooth; 2a, minor movement or respiratory upset; 2b, moderate upset; and 3, unacceptable. Patients breathed spontaneously and were given a mixture of 60% nitrous oxide in oxygen supplemented by 1%–1.5% isoflurane from a mask and a semiclosed circuit system with a fresh gas flow of 50 mL·kg⁻¹·min⁻¹. The isoflurane concentration was maintained between 1% and 1.5%. At the end of the operation, the administration of anesthetics was discontinued, and the time to eye opening and orientation were recorded.

In the recovery room, heart rate and arterial blood pressure were recorded at 5-min intervals for 1 h. Postoperative sedation was assessed at 5 and 10 min, and patients completed a Treiger test at 30 min and a VAS for pain at 15, 30, 60, and 90 min postoperatively. The CFF readings were recorded at 30, 60, and 90 min. The incidence of nausea, vomiting, and dry mouth was noted.

Results are shown as the mean ± SD for parametric data and mean + range for nonparametric data. Statistical analysis was by analysis of variance, *t*-test, and χ^2 -test for parametric data and by Kruskal-Wallis and Mann-Whitney U test for nonparametric data. Statistical significance was accepted at *P* < 0.05.

Results

One hundred patients, divided into four equal groups (according to pretreatment given: temazepam, clonidine, timolol, and placebo), were studied. Demographic data were comparable in all four groups, as was the duration of anesthesia (Table 1).

There were no significant differences between the four groups in preinduction scores. Although the sedative properties of both clonidine and temazepam are well documented, only three patients in each of these groups were assessed as either drowsy or asleep. One patient in the timolol group was drowsy, and all the patients in the placebo (control) group were awake. No patients were judged to be unable to

Table 1. Demographic Data

	Temazepam	Clonidine	Timolol	Placebo
Age (yr)	32 ± 10	32 ± 8	32 ± 10	30 ± 8
Weight (kg)	77.6 ± 11	75.8 ± 11	74.6 ± 12	74.9 ± 13
Sex (M/F)*	20/5	19/6	18/7	18/7
Duration (min)	45 ± 8	42 ± 11	43 ± 9	42 ± 12

Values are mean ± SD.

*Number of male and female patients.

Table 2. Anxiety Scores Before and After Premedication

	Before	After
Temazepam	30 (5–84)	26 (1–65)*
Clonidine	25 (3–92)	24 (4–61)*
Timolol	28 (7–92)	30 (24–100)*
Placebo	29 (4–81)	66 (29–100)

Values are mean (range).

**P* < 0.05 compared with placebo.

complete VAS scores owing to their sedated condition.

Baseline anxiety scores were similar for all groups. After premedication, all the active treatments (temazepam, clonidine, timolol) produced significantly lower scores than the inert treatment (placebo) did (*P* < 0.01); however, the scores were not significantly reduced compared with pretreatment values (Table 2). There were no significant differences between the groups given active treatments.

The requirements for propofol were significantly reduced in all active treatment groups compared with the inert treatment (temazepam, 2.2 ± 0.3 mg/kg; clonidine, 2.2 ± 0.3 mg/kg; timolol, 2.2 ± 0.4 mg/kg; placebo, 2.8 ± 0.7 mg/kg), and differences between the treated groups did not reach significant levels.

Patients in the active-treatment groups had a significantly smoother induction of anesthesia compared with the placebo group. In the clonidine group, all the inductions were graded as either 1 or 2a. Four patients in the placebo group had grade 3 induction, with one patient requiring muscle relaxation and endotracheal intubation to maintain airway control. All the inductions graded as 2b or 3 were on the basis of breath-holding and respiratory difficulties (Table 3).

Preoperative cardiovascular readings were similar in all the groups. Compared with baseline values, mean arterial pressure was significantly less only in the timolol group during the period before skin incision. However, on between-group analysis, there were no significant differences in any of the groups, and no patients required treatment for clinical hypotension (Table 4).

Compared with both baseline values and on between-group analysis, heart rate was also signifi-

Table 3. Induction Grades

Grade	Number of patients			
	Temazepam	Clonidine	Timolol	Placebo
1	13	11	16	6
2a	10	14	5	8
2b	2	0	4	7 ^a
3	0	0	0	4 ^a

^a*P* < 0.05 compared with other groups.**Table 4.** Mean Arterial Blood Pressure Readings

	Temazepam	Clonidine	Timolol	Placebo
Preinduction	87 ± 12	89 ± 15	88 ± 14	86 ± 9
+5 Min	83 ± 15	82 ± 14	71 ± 16 ^a	83 ± 12
+10 Min	84 ± 16	84 ± 12	71 ± 12 ^a	81 ± 12
Skin incision	90 ± 15	84 ± 15	80 ± 11	82 ± 11
+10 Min	90 ± 14	88 ± 12	83 ± 12	82 ± 11
+20 Min	87 ± 11	86 ± 12	83 ± 12	82 ± 10
Recovery	93 ± 10	87 ± 9	86 ± 10	83 ± 9

Values are given in millimeters of mercury and are mean ± SD.

^a*P* < 0.05 compared with preinduction values.**Table 5.** Heart Rate Readings

	Temazepam	Clonidine	Timolol	Placebo
Preinduction	75 ± 12	74 ± 11	75 ± 10	73 ± 12
+5 Min	75 ± 11	73 ± 12	60 ± 11 ^{a,b}	72 ± 13
+10 Min	75 ± 13	69 ± 14	62 ± 10 ^a	71 ± 15
Skin incision	75 ± 13	71 ± 15	64 ± 10	72 ± 13
+10 Min	70 ± 13	70 ± 13	63 ± 12	69 ± 14
+20 Min	69 ± 11	69 ± 13	64 ± 14	69 ± 10
Recovery	73 ± 9	70 ± 8	70 ± 10	70 ± 8

Values are given in beats per minute and are mean ± SD.

^a*P* < 0.05 compared with preinduction values.^b*P* < 0.05 compared with other groups.

cantly lower in the timolol group during the period after induction and before skin incision. Four patients (two in the timolol group and one in each of the temazepam and clonidine groups) (Table 5) required intravenous atropine for a heart rate of less than 45 beats/min.

Tissue oxygen saturation readings were within normal limits in all the patients, and there were no differences between the groups.

Sedation scores 5 min postoperatively were similar in all four groups, with 60%, 62%, 58%, and 56% of patients being sedated in the temazepam, clonidine, timolol, and placebo groups, respectively. However, at 10 min, the clonidine group had a significantly higher number of sedated patients (28%) compared with 12%–16% in the other groups.

The time to recovery, recorded as the time to eye opening and orientation, was significantly shorter in the timolol and placebo groups compared with that of

Table 6. Postoperative Recovery Time and Critical Flicker Frequency

	Temazepam	Clonidine	Timolol	Placebo
Eye opening (min)	9.0 ± 3	10.4 ± 3	7.9 ± 3 ^a	8.1 ± 4 ^a
Orientation (min)	12.9 ± 3	12.8 ± 3	10.3 ± 3 ^{a,b}	10.6 ± 4 ^{a,b}
CFF at 30 min (Hz)	-2.5 ± 3	-3.4 ± 3	-0.6 ± 3 ^{a,b}	-2.0 ± 3
CFF at 60 min (Hz)	-2.1 ± 3	-3.3 ± 3	-1.1 ± 2 ^a	-2.5 ± 3

CFF, critical flicker frequency is given as maximum change from baseline values.

Values are mean ± SD.

^a*P* < 0.05 compared with clonidine.^b*P* < 0.05 compared with temazepam.**Table 7.** Visual Analogue Scoring System Scores for Pain Postoperatively

	Temazepam	Clonidine	Timolol	Placebo
15 Min	31 (0-62) ^a	34 (0-75) ^a	48 (1-89)	54 (4-99)
30 Min	32 (1-74) ^a	34 (1-78) ^a	44 (0-80)	47 (7-80)
60 Min	28 (1-70)	30 (1-68)	31 (4-69)	34 (2-74)
90 Min	26 (1-59)	27 (0-76)	29 (4-65)	30 (1-68)

Values are mean (range).

^a*P* < 0.05 compared with timolol and placebo groups.

the temazepam and clonidine groups (*P* < 0.05). There were no significant differences between the clonidine and temazepam groups (Table 6).

On assessment of the change from baseline in the CFF readings at 30 min, both the clonidine and temazepam groups had significant increases compared with that of the timolol group. At 60 min, there was only a difference between the clonidine and timolol groups. By 90 min, there were no differences between the groups (Table 6). There were no significant differences among the groups in the Treiger test either preoperatively or postoperatively.

At 15 and 30 min, the temazepam and clonidine groups had lower VAS scores for pain. By 60 min, there were no significant differences among the groups (Table 7). The number of patients requesting analgesia postoperatively was similar in the four groups (six in the temazepam and clonidine groups, seven in the timolol group, and eight in the placebo group).

The incidence of emetic symptoms was low with only one patient in each of the clonidine, timolol, and placebo groups, and two in the temazepam group. The differences were not significant.

In the clonidine group, four patients complained of a dry mouth preoperatively that persisted into the recovery period. Four patients in the timolol group and five in the placebo group became emotionally

disinhibited in the recovery room, a phenomenon previously described with propofol anesthesia (13). This did not occur in the clonidine and temazepam groups. There were no other significant side effects.

Discussion

The choice of doses in this study was based on a number of factors. Temazepam, 20 mg, is accepted as satisfactory premedication for minor surgery and clonidine, 0.2 mg, produces marked anxiolysis with minimal cardiovascular disturbance (14). Timolol, 10 mg, provides anxiolysis without significant hypotensive effects (4). The onset of action of all three oral preparations occurs between 60 and 90 min, with all three preparations having a half-life in plasma of longer than 3 h. The plasma concentrations of the active drugs should, therefore, have been within the therapeutic limits during the study period.

Compared with the placebo, all three active treatments resulted in less anxiety in the preinduction period, and there were no significant differences between the active treatment groups. The sedative properties of clonidine and temazepam have been well documented by other workers (15,16); but in this study, there were no differences between the active and inert treatments. The reason is unclear but may be due to the fact that all the patients were fit and healthy and tended to be athletic men who may be more resistant to the sedative effects of drugs. Other workers have noted a significant decrease in anesthetic requirements with clonidine (17); but in most cases, the comparison was with an inert treatment. This study agrees that the decrease noted was significant compared with the placebo group, but not compared with the other active treatments. As expected, all subjects in the active-treatment groups had a smoother induction of anesthesia compared with the inert group. Clonidine, by decreasing central sympathetic outflow, reduces arterial blood pressure and heart rate by up to 15% in normotensive patients (18). Although cardiovascular effects are dose-related (19), 0.2 mg of clonidine produces minimal changes (14). Here, timolol was the only drug that significantly decreased arterial blood pressure and heart rate from preoperative values, although there were no significant differences among the groups and there was no clinical hypotension. Many of the patients studied were fit athletes with low baseline heart rates; and in this population group, a heart rate of 45 beats/min may not normally require treatment with atropine.

Timolol resulted in faster recovery of patients in the early postoperative period; but by 90 min, there was no difference between the groups. The advantages of this are not marked as even day-case patients

are rarely required to be up and about within 90 min. Patients receiving clonidine were more sedated postoperatively, and the larger degree of sedation was reflected in the differences in the CFF readings. Critical flicker frequency measures the ability to distinguish discrete sensory information and is an index of cortical activity (20). The test is a good indicator of the action of sedative drugs (21) and has the advantage over other methods of being easy to administer and has little practice effect. After treatment with clonidine, readings were slowest to return to baseline values. Timolol resulted in a more rapid patient recovery than placebo did, which may be a reflection of the larger requirements for propofol in the placebo group. The Treiger dot test is used as a test of sensory motor disturbances, as it may be altered by central nervous system depressants (22). Here, none of the groups showed marked changes in the recovery period compared with baseline values, and there were no significant differences between the groups despite the slower recovery in the clonidine-treated patients.

Although the analgesic properties of clonidine are well documented (23), the VAS scores for pain in this group were similar to those in the temazepam group. Oral clonidine may not have significant analgesic properties compared with the extradural route. The dry mouth after oral clonidine pretreatment is a dose-related side effect (24) that may render clonidine unacceptable for routine premedication. The absence of disinhibition in the clonidine and temazepam groups may be related to their sedative effects and to the longer recovery time. Although clinically it is not a disadvantage, it makes the early supervision of patients more difficult.

Although timolol and clonidine may have specific indications for use preoperatively, for routine use they offer no additional benefits to those obtained currently with the benzodiazepines and are unlikely to be used widely in the field of premedication.

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Life-Threatening Hypocalcemia After Abdominal Aortic Aneurysm Repair in Patients With Renal Insufficiency

Richard C. Prielipp, MD, and Gary P. Zaloga, MD

Department of Anesthesia, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, North Carolina

Hypocalcemia is recognized by a variety of clinical signs and symptoms related to neuromuscular irritability (tetany, muscle spasm, weakness), irritability of the respiratory tract (laryngeal spasm, bronchospasm), psychiatric instability (anxiety, dementia, psychosis), and cardiovascular impairment (hypotension, decreased contractility, bradycardia) (1,2). However, many of these signs are obscured by general anesthesia (2). As a result, cardiovascular insufficiency may be the only observable feature of hypocalcemia in anesthetized or unresponsive critically ill patients (3).

Although ionized hypocalcemia develops in 15%–20% of critically ill patients, it is usually mild (i.e., 0.80–1.0 mmol/L) and without hemodynamic sequelae (3,4). Nonetheless, hypocalcemia must still be considered in the differential diagnosis of hypotensive patients who are refractory to intravenous fluid resuscitation and administration of cardiovascularly active drugs. Ionized hypocalcemia ($[Ca] < 1.0$ mmol/L) may result from impaired parathyroid hormone secretion, impaired vitamin D synthesis or action, calcium precipitation or chelation, and decreased bone calcium mobilization. Patients with renal insufficiency may be at increased risk for developing hypocalcemia because of their impaired ability to mobilize skeletal calcium secondary to parathyroid hormone or vitamin D deficiency (3). We present two patients with renal insufficiency in whom life-threatening hypocalcemia complicated their recovery from abdominal aortic aneurysm repair.

Case 1

An 89-yr-old, 55-kg woman was admitted with a 2-wk history of epigastric fullness and sharp lower back pain. Her past medical history included 30 yr of essential arterial hypertension controlled by chlortha-

lidone and reserpine. She had no cardiac or respiratory symptoms, and her only previous surgery was for repair of a hip fracture under general anesthesia without complications. An 8-cm abdominal aortic aneurysm was diagnosed by angiography.

Laboratory data collected before aneurysmectomy included the following values: hematocrit, 34.7%; serum creatinine, 168 μ mol/L (1.9 mg/dL); and blood urea nitrogen, 8.9 mmol/L (25 mg/dL) (estimated creatinine clearance = 21.0 mL/min based on age, weight, and serum creatinine) (5). Serum electrolytes and liver function tests were normal. Serum albumin was 35 g/L (normal, 32–50 g/L) and total serum calcium was 2.25 mmol/L (9.0 mg/dL). The electrocardiogram was remarkable for left ventricular hypertrophy and a prolonged QT interval (480 ms at a rate of 56 beats/min; the corrected QT interval was 456 ms).

In the operating room, arterial and pulmonary artery catheters were inserted under local anesthesia. Induction of general anesthesia was accomplished by intravenous fentanyl (20 μ g/kg), midazolam (0.1 mg/kg), metocurine (0.2 mg/kg), and pancuronium (0.05 mg/kg). After orotracheal intubation, general anesthesia was maintained with oxygen, air, and halothane (0.2%–0.4% end-tidal concentration). Additional incremental doses of intravenous fentanyl (50–100 μ g) were administered as indicated by heart rate or arterial blood pressure.

Brisk bleeding was encountered during the dissection of the extensive infrarenal aneurysm. To correct the diminished urine output and blood loss, dopamine was infused ($2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) with 10 U of citrated packed red blood cells. In addition, 500 mL of 5% albumin, 50 mL of 25% albumin, and 8 L of lactated Ringer's solution were infused for intravascular volume replacement. During the time of aortic cross-clamping, analysis of arterial blood with an (FiO_2) of 0.6 was $\text{pH}_a = 7.36$, arterial O_2 tension (PaO_2) = 32.9 kPa (247 mm Hg), arterial CO_2 tension (PaCO_2) = 5.2 kPa (39 mm Hg), hematocrit = 37%, and ionized calcium = 0.95 mmol/L (normal 1.0–1.2 mmol/L). Estimated blood loss at the time of aortic unclamping was 7000 mL. After unclamping of the

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Address correspondence to Dr. Prielipp, Department of Anesthesia, Bowman Gray School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1009.

Table 1. Intraoperative Calcium Concentrations and Hemodynamic Disturbances in Patient 1

Variables	Preinduction	Postinduction	Ao X-C placed	Ao X-C removed	After IV CaCl ₂
Total Ca (mg/dL)	9.0	—	—	—	—
Ionized Ca (mmol/L)	—	1.13	0.93	0.50	0.81
Heart rate (beats/min)	80	70	86	80	76
Blood pressure (mm Hg)	170/90	120/70	150/80	96/60	140/80
Cardiac output (L/min)	—	4.6	3.9	3.3	4.5
Pulmonary artery occlusion pressure (mm Hg)	—	13	18	22	19

Ca, calcium; Ao X-C, aortic vascular cross-clamp; IV, intravenous.

aorta, an additional 3-U blood transfusion was required over the next 45 min. Despite satisfactory analysis of arterial blood gases (pHa = 7.35, Pao₂ = 30.9 kPa [232 mm Hg], Paco₂ = 4.5 kPa [34 mm Hg]), arterial blood pressure decreased and became refractory to intravenous fluid resuscitation (pulmonary artery occlusion pressure = 18–22 mm Hg). A phenylephrine infusion was required to maintain systolic blood pressure >95 mm Hg. Ventricular premature contractions were suppressed with a lidocaine infusion. Repeat laboratory determinations at this time revealed hematocrit = 35% and ionized calcium = 0.50 mmol/L. Intravenous bolus administration of CaCl₂ (250 mg × 3) effectively increased cardiac output and arterial blood pressure (Table 1), eliminating the need for phenylephrine infusion. Thereafter, the arterial blood pressure stabilized at 140/80 mm Hg without vasoactive infusions, and the cardiac output increased by 30% (Table 1). Calcium levels (0.81 mmol/L after CaCl₂ administration) and hemodynamic variables remained stable throughout the remainder of the operation, and the patient was taken to the critical care unit without further problems.

Case 2

A 69-yr-old man with recent onset of moderate renal insufficiency, abdominal pain, and a history of an abdominal aortic aneurysm was admitted to the hospital for evaluation. He had a history of essential arterial hypertension for which he was treated with clonidine (0.2 mg twice a day). Physical examination revealed arterial blood pressure = 190/100 mm Hg and heart rate = 100 beats/min. Preoperative laboratory findings included: hemoglobin = 12.0 g/L, white blood cell count = 16,900/mm³, platelet count = 205,000/mm³, Na = 130 mmol/L, K = 4.5 mmol/L, blood urea nitrogen = 32.1 mmol/L (90 mg/dL), creatinine = 680 μmol/L (7.7 mg/dL), glucose = 18.2 mmol/L (328 mg/dL), albumin = 42 g/L, total Ca = 2.37 mmol/L (9.5 mg/dL), PO₄ = 1.58 mmol/L (4.9 mg/dL), and Mg = 1.11 mmol/L (2.7 mg/dL).

Electrocardiogram showed a normal sinus rhythm and normal QT interval. He was found to have an enlarging aortic aneurysm and was scheduled for aneurysmectomy.

In the operating room, a leaking abdominal aortic aneurysm was repaired after induction of general anesthesia with intravenous fentanyl (25 μg/kg), vecuronium (0.12 mg/kg), N₂O (50%), and isoflurane (0.2%–1.0% end-tidal concentration). During surgery, brisk blood loss estimated at 3–4 L was replaced with 9 L of normal saline and 6 U of whole blood. The patient was transferred to the critical care unit with his trachea intubated. Analysis of arterial blood gases (Fio₂ = 0.50) disclosed a pHa = 7.25, Pao₂ = 10.6 kPa (80 mm Hg), and Paco₂ = 5.33 kPa (40 mm Hg). Thereafter, progressive hypotension (mean arterial pressure decreased to 60 mm Hg), oliguria (10 mL/h), and metabolic acidosis (pHa = 7.15–7.25) developed. Cardiac index was 2.0 L·min⁻¹·m⁻². Over the next several hours, 10 L of normal saline, 250 mL of 5% albumin, and 250 mL of blood were administered to improve cardiac preload and urine output. Dopamine (initially 2 μg·kg⁻¹·min⁻¹) was increased to 15 μg·kg⁻¹·min⁻¹; however, cardiac index (2.4 L·min⁻¹·m⁻²) and mean arterial blood pressure (72 mm Hg) responded poorly. Repeat analysis of arterial blood gases (Fio₂ = 0.5, peak end-expiratory pressure = 0 cm H₂O) indicated pHa = 7.22, Pao₂ = 9.7 kPa (73 mm Hg), and Paco₂ = 5.9 kPa (44 mm Hg). Intravenous sodium bicarbonate (132 mmol over 3 h) was administered to maintain pHa > 7.25. After the last ampule of intravenous sodium bicarbonate, the patient developed bradycardia progressing to asystole. Resuscitation attempts were unsuccessful. Blood ionized calcium (drawn anaerobically from an arterial heparinized sample) at the time of cardiac arrest was 0.5 mmol/L. Total serum calcium = 1.17 mmol/L (4.7 mg/dL), PO₄ = 2.49 mmol/L (7.7 mg/dL), Mg = 1.03 mmol/L (2.5 mg/dL), and K = 4.3 mmol/L. Postmortem examination demonstrated normal coronary arteries and

no evidence of myocardial necrosis. The pancreas was edematous but not inflamed.

Further laboratory investigations were initiated from blood samples taken at the time of this cardiac arrest. Serum magnesium was normal (1.0 mmol/L) and an n-terminal parathyroid hormone level (from plasma obtained just before the arrest) was 57 pg/mL, two to three times normal (11–24 pg/mL). However, a calcitriol (1,25-dihydroxyvitamin D) level was *undetectable* in the face of a normal calcidiol (25-hydroxyvitamin D) level.

Discussion

Calcium is required for normal hormonal secretion, enzyme activity, blood coagulation, muscle excitation-contraction coupling, cardiac action potential, and cardiac contraction (1,2). The direct measurement of *ionized* calcium, the physiologically active and regulated fraction, remains the best clinical measure of calcium activity in critically ill patients (1,6). Regulation of ionized calcium is accomplished through the combined effects of parathyroid hormone and vitamin D on bone. Parathyroid hormone deficiency may result from parathyroid gland injury or suppression of parathyroid hormone by hypercalcemia, hypomagnesemia, hypermagnesemia, or feedback regulation by calcitriol (1,25-dihydroxyvitamin D) (2). Vitamin D is synthesized in the skin or absorbed by the gut. Vitamin D is 25-hydroxylated in the liver and then 1-hydroxylated in the kidneys to its most active form, calcitriol. Thus, disease of the kidneys or liver may impair vitamin D activation and thereby disrupt normal calcium homeostasis. We now report the occurrence of life-threatening perioperative hypocalcemia associated with renal insufficiency in two patients, and documented deficiency of 1,25-dihydroxyvitamin D in one patient. We hypothesize that significant renal dysfunction may predispose patients to hypocalcemia during acute surgical stress.

Severe ionized hypocalcemia was noted in our first patient approximately 30 min after removal of the aortic cross-clamp. Possible causes of the hypocalcemia in this patient include depressed parathyroid hormone secretion, decreased 1-hydroxylation of vitamin D secondary to mild renal insufficiency, calcium chelation owing to rapid administration of albumin or citrated blood, bicarbonate administration (increased pH_a causing calcium to bind more avidly to albumin), and hemodilution owing to infusion of calcium-free replacement fluids. Common calcium chelators encountered in the operating room are citrate (in blood products) and albumin. However, massive blood transfusion is generally required (>100 mL/min of citrated blood) to cause important degrees of hypocalcemia (7). Calcium binding to

albumin varies greatly between patients (from 0.2 to 1.2 mg·dL⁻¹·g albumin⁻¹) and no reliable correction factor can be calculated for such changes in albumin levels. In experimental models, hemodilution alone (hematocrit diluted from 43% to 14% over 2 h) with lactated Ringer's solution did not result in hypocalcemia (8). Thus, the majority of experimental evidence suggests that calcium homeostatic mechanisms should maintain normal ionized calcium concentrations despite the documented operative stress.

Similarly disturbed ionized calcium concentrations were encountered in the second patient. He received large volumes of calcium-free fluids (9 L of normal saline), and chelation to exogenous albumin and phosphorus (serum PO₄ = 7.7 mg/dL) further reduced ionized calcium. Nonetheless, the parathyroid hormone concentration indicates an appropriate parathyroid secretory response to developing hypocalcemia. However, the calcitriol (1,25-dihydroxyvitamin D) concentration was undetectable in the face of a normal calcidiol (25-hydroxyvitamin D) concentration, presumably secondary to renal failure (because the 1-hydroxylase enzyme, which converts calcidiol to calcitriol, is located in renal tissue) (9). This inability to synthesize calcitriol predisposes patients with renal failure to ionized hypocalcemia.

Our data indicate that patients with renal insufficiency undergoing aortic aneurysm repair and perhaps other surgical procedures may be at high risk for developing life-threatening hypocalcemia. The hypocalcemia results from impaired calcitriol synthesis, use of calcium-free fluids, use of chelators such as citrated blood and albumin, and use of bicarbonate to treat metabolic acidoses. Hypomagnesemia or hypermagnesemia may also contribute to hypocalcemia as a result of parathyroid gland suppression. It is important to monitor ionized calcium in patients at risk for hypocalcemia and to treat life-threatening hypocalcemia. Surgeons and anesthesiologists should be aware of the uniquely increased risk for ionized hypocalcemia in these patients.

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Remote Asynergy Detected by Biplane Transesophageal Echocardiography During Myocardial Revascularization Without Cardiopulmonary Bypass

Randall M. Schell, MD, Pratima M. Shah, MD, Richard L. Applegate II, MD, Pravin M. Shah, MD, and Carlos A. Schmidt, MD

Departments of Anesthesiology, Cardiology, and Cardiovascular Surgery, Loma Linda University, Loma Linda, California

In 1935, Tennant and Wiggers (1) demonstrated that the mechanical sequelae of acute coronary artery occlusion was myocardial muscle lengthening rather than shortening during systole. Subsequently, abnormal left ventricular regional wall motion and systolic wall thickening detected echocardiographically have been recognized as sensitive and early indicators of ischemia (2).

In the paradigm of myocardial ischemia that might occur intraoperatively, standard methods of cardiac monitoring (electrocardiographic and hemodynamic) are indirect and potentially inaccurate (3). Two-dimensional transesophageal echocardiography (TEE) has made continuous echocardiographic monitoring possible throughout an operative procedure (4). Moreover, with the recent introduction of biplane TEE (5), not only the standard midpapillary short axis view but also its corresponding longitudinal cross section of the left ventricle may be monitored. Despite these advancements, human echocardiographic studies of left ventricular function performed before and immediately after acute coronary occlusion have been limited to short periods (30–75 s) of ischemia during coronary artery balloon angioplasty (6).

In our Medical Center, myocardial revascularization is selectively performed without cardiopulmonary bypass (CPB) (7,8). The following case demonstrates the acute effects of coronary artery occlusion (13 min) and reperfusion on ventricular wall kinesis as detected by biplane TEE.

Case Report

A 67-yr-old, 62-kg female patient with a 15-yr history of angina but with no documented myocardial infarctions was scheduled for three-vessel myocardial revascularization. Physical examination was notable for an arterial blood pressure of 200/104 mm Hg and an S₄ heart sound. The electrocardiogram (ECG) showed left ventricular hypertrophy with repolarization abnormality. Preoperative coronary angiography demonstrated a dominant right system with 75% proximal left anterior descending artery (LAD) stenosis and 100% proximal right coronary artery occlusion with extensive collaterals from distal LAD branches (Figure 1). The left ventriculogram demonstrated an ejection fraction of 0.66 with symmetric contraction.

The patient was premedicated with morphine sulfate and lorazepam. A 20-gauge radial arterial catheter, a five-lead electrocardiogram, and a pulse oximeter were placed on the patient's arrival at the operating room. Leads II and V₅ of the ECG were continuously monitored. Induction of anesthesia was accomplished with the intravenous administration of 30 µg/kg of fentanyl and inhalation with 2% (mixed expired) enflurane through a mask. A pancuronium and metocurine combination was given intravenously to facilitate tracheal intubation with stable hemodynamic variables.

A 5.0-MHz biplane echocardiographic probe (ALOKA systems) was positioned in the esophagus to obtain cross sections of the left ventricle. The transverse plane provided the short axis of the left ventricle at the midpapillary muscle level, and the longitudinal plane gave a nearly orthogonal cross section along the long axis of the left ventricle. Wall motion was symmetrical (Figure 2). Anesthesia was maintained with fentanyl (50 µg/kg before sternotomy) and enflurane (0.2%–0.75%) titrated to arterial blood pressure. A pulmonary artery catheter was

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Address correspondence to Dr. Applegate, Department of Anesthesiology, Loma Linda University Medical Center, Loma Linda, CA 92354.

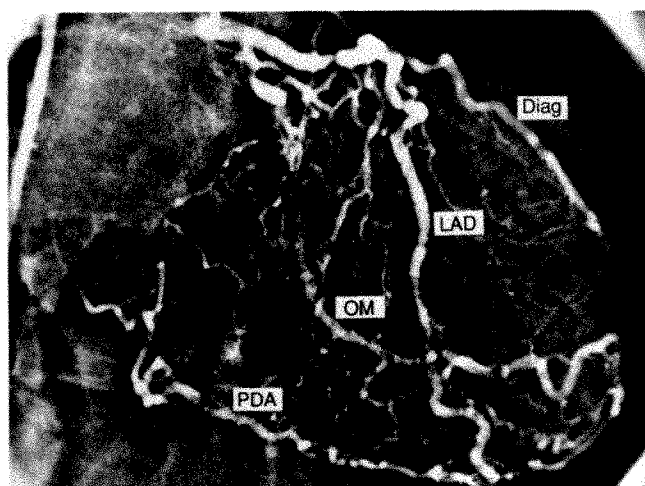
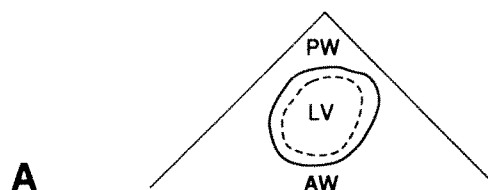
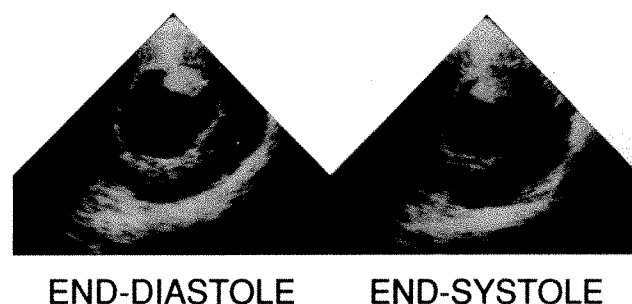
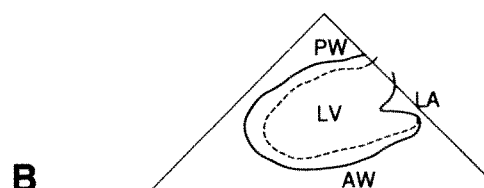
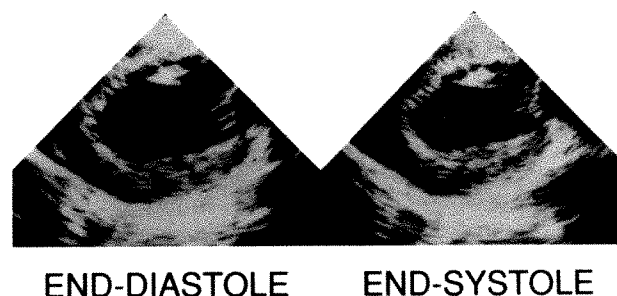


Figure 1. Coronary angiogram. Left coronary injection demonstrating collateral filling of the posterior descending (PDA) and circumflex artery territories. LAD, left anterior descending artery; OM, obtuse marginal branch; Diag, diagonal branch.

introduced through the right internal jugular vein (thermodilution cardiac output, 3.4 L/min; pulmonary artery pressure, 14/7 mm Hg; pulmonary artery occlusion pressure, 7 mm Hg). Heparin (10,000 U) was given before revascularization without CPB. Approximately 20 s after occlusion of the LAD, the arterial blood pressure decreased (from 145/80 to 130/70 mm Hg), heart rate increased (from 80 to 90 beats/min), and cardiac output decreased (from 3.4 to 2.5 L/min). The ECG, pulmonary artery pressure, and pulmonary artery occlusion pressure did not change. However, biplane TEE demonstrated asynergy involving the posteroseptal, anteroapical, anteroapical, posterobasal, inferior wall, and inferoapical segments. The basal and midsegments of the anterior wall showed normal motion. Asynergy consisted of akinesia in all areas except for dyskinetic apical and anteroapical segments (Figure 3). A nitroglycerin infusion was begun ($2 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), and esmolol was titrated to maintain the heart rate between 70 and 80 beats/min. Myocardial asynergy lasted throughout LAD occlusion (13 min) with full recovery of wall motion within 3–4 min of reperfusion. Heart rate and cardiac output also returned to baseline. Revascularization of the obtuse marginal and diagonal was completed without complications. After complete revascularization, the cardiac output was 3.5 L/min and the pulmonary artery pressure was 16/10 mm Hg. No acute changes were observed in lead II or V₅ of the ECG. The trachea was extubated within 11 h; and excluding several episodes of supraventricular tachycardia, the postoperative course was unremarkable. The concentration of cardiac isoenzymes was not elevated and the ECG was unchanged. The patient



A



B

Figure 2. Biplane TEE. Transverse (A) and longitudinal (B) planes demonstrate symmetrical wall motion before LAD occlusion (control). AW, anterior wall; LA, left atrium; LV, left ventricle; PW, posterior wall; ---, end systole; —, end diastole.

was discharged on postoperative day 6 and has remained angina-free.

Discussion

The effects of acute coronary artery occlusion on ventricular wall motion have been demonstrated in dogs. Within 30 s of complete coronary occlusion, wall motion changes are detected. When occlusion is maintained for less than 15 min, ischemic electrocardiographic changes recover rapidly without permanent myocardial injury. However, myocardial function in the ischemic zone can remain depressed for hours (9,10). Changes in left ventricular function

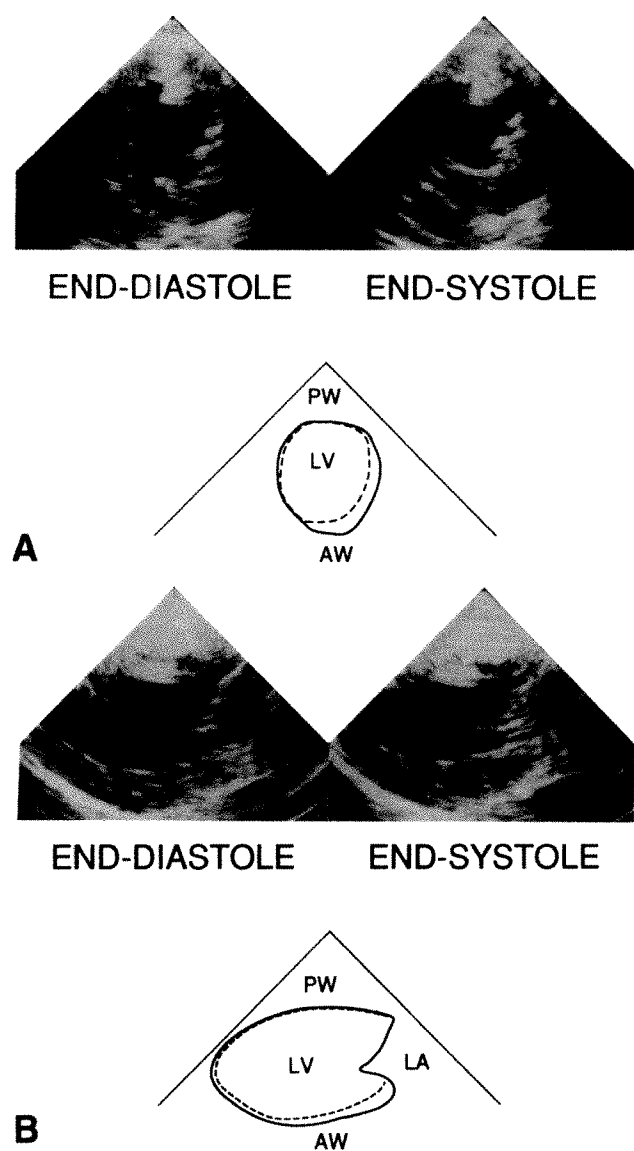


Figure 3. Biplane TEE. Transverse (A) and longitudinal (B) planes demonstrate wall motion changes with LAD occlusion. AW, anterior wall; LA, left atrium; LV, left ventricle; PW, posterior wall; ---, end systole; —, end diastole.

resulting from ischemia can be demonstrated in humans during acute myocardial infarction, stress-induced angina, and balloon occlusion of a coronary artery during angioplasty. Echocardiography performed during coronary artery angioplasty has shown decreased wall thickening, endocardial velocity, and wall motion of the ischemic zone occurring within 15–20 s of arterial occlusion and resolving within 10–20 s of balloon deflation (6).

We have extensively used the TEE probe in midesophageal position intraoperatively to provide four-chamber and two-chamber cross sections using transverse and longitudinal planes, respectively. We consider the midesophageal planes to be particularly

useful in most monitoring situations. In this patient, however, the transgastric imaging cross sections were used as per standard practice in our early experience. Biplane echocardiographic monitoring was continued throughout the time of coronary occlusion and reperfusion. The wall motion abnormalities observed on occlusion of the LAD were extensive and involved the territories normally perfused by the dominant right coronary artery. One may surmise that these territories were subserved by major collateral flow from the LAD and its branches. Echocardiographic findings during the clamp period showed the myocardium at risk by detecting asynergy. The transverse cross section used in the monoplane TEE did provide evidence of ischemia in the posteroinferior segment at the level of the papillary muscles. However, the longitudinal plane provided a more accurate assessment of the extent of asynergy involving the entire length of the posteroinferior wall including the apex. We believe the biplane probe to be superior in permitting visualization of the apex, which is frequently involved in ischemic asynergy. The single-plane TEE may or may not permit visualization of the apex, depending on orientation of the heart in relation to the fundus of the stomach. Moreover, despite these extensive wall motion changes, real-time electrocardiographic monitoring of leads II and V₅ did not demonstrate ischemic changes. Despite 13 min of total LAD occlusion, complete recovery of segmental asynergy occurred within 3 to 4 min of reperfusion.

The use of TEE throughout revascularization may allow appropriate fluid and pharmacologic interventions to reduce the workload of the heart and to improve the myocardial oxygen supply-demand ratio. Moreover, it allows early detection of severe multiple wall motion changes or ventricular dilatation on initial test occlusion of the coronary artery, suggesting the need for standard CPB support. In this case, an esmolol infusion was begun before coronary artery occlusion as a slower heart rate facilitates coronary revascularization on a beating heart. With LAD occlusion and evidence of segmental asynergy on TEE, a nitroglycerin infusion was begun. However, the segmental asynergy persisted until after reperfusion.

The benefits of TEE monitoring include a detector of ischemia more sensitive than the ECG (3) and hemodynamic monitoring and a capability to evaluate wall motion in areas revascularized. Echocardiographic findings before and after myocardial revascularization using CPB have demonstrated no change or decrease in segmental function, whereas other methods have noted improvement. However, the importance of postbypass regional wall motion abnormali-

ties as a predictor of an adverse clinical outcome has been documented (11-13).

In the unique setting where myocardial revascularization is performed without CPB and where a coronary artery is occluded, TEE demonstrates the immediate effects of reduced flow on ventricular kinesis. A recent echocardiographic study of six patients and occlusion of 11 coronary arteries during myocardial revascularization without CPB demonstrated that the time to full recovery is related to the duration of coronary occlusion (14). However, despite the longest total coronary occlusion time of 27 min, the maximal time to full recovery of segmental asynergy was only 306 s.

In summary, biplane TEE documented the effects of acute coronary artery occlusion and reperfusion on ventricular wall motion. It demonstrated ventricular asynergy in the territory normally supplied by the right coronary artery on occlusion of the LAD. Despite 13 min of LAD occlusion, wall motion fully recovered within 3 to 4 min with no postoperative evidence of myocardial damage.

Transesophageal echocardiography may be an important component of monitoring for patients undergoing myocardial revascularization without CPB.

We thank T. Hozumi, MD, for technical assistance.

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Reexpansion Pulmonary Edema After Mediastinal Tumor Removal

Naoki Matsumiya, MD, Shuji Dohi, MD, Tetsu Kimura, MD, and Hiroshi Naito, MD

Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Tsukuba City, Ibaraki, Japan and Department of Anesthesiology, Gifu University School of Medicine, Gifu City, Gifu, Japan

Sudden evacuation of pneumothorax or pulmonary effusion may cause edema of ipsilateral lung (reexpansion pulmonary edema, RPE) (1). Other reports described a more acute form of RPE associated with lung reexpansion after several hours of atelectasis (2,3). Can lung reexpansion after one-lung ventilation cause the edema formation of the nondependent lung? We describe a case of RPE that developed immediately after the removal of a mediastinal tumor during one-lung ventilation anesthesia in a young patient.

Case Report

A 17-yr-old boy (body weight 58 kg, height 166 cm) was admitted to the hospital because he experienced a sudden sharp pain in his right hemithorax. Chest roentgenogram (Figure 1) and computed tomograph demonstrated an anterior mediastinal tumor, which was scheduled for removal. His serial chest roentgenograms revealed an increase in the size of the mediastinal tumor and partial atelectasis of the right lower lung and atelectasis of the right middle lobe. His electrocardiogram showed right axis deviation. His echocardiogram demonstrated the adjacency of the tumor to the right ventricle. Analysis of arterial blood gases with a fraction of inspired O_2 of 0.2 disclosed the following values: pHa 7.39, arterial O_2 tension 78 mm Hg, and arterial CO_2 tension 39 mm Hg. His preoperative pulmonary function studies revealed a forced vital capacity of 3.74 L and a forced expiratory volume in 1 s of 2.91 L. The data of other laboratory tests were unremarkable.

Diazepam (10 mg) was given orally 90 min before arrival in the operating room. After the intravenous injection of 100 μ g of fentanyl, his cervical epidural space was punctured with a 17-gauge Tuohy needle

at the C7-T1 intervertebral space, and an epidural catheter was inserted into which 8 mL of 2% lidocaine with epinephrine (1:200,000) was injected. Then general anesthesia was intravenously induced with 300 mg of thiamylal and 100 μ g of fentanyl. The trachea and left main bronchus were intubated with a 35F, left-sided, double-lumen endobronchial tube (Bronchocath, National Catheter, New York, N.Y.). The appropriate placement of the endobronchial tube was confirmed with chest auscultation and fiberoptic bronchoscopic examination. The narrowing of the right main bronchus owing to compression by the mediastinal tumor was observed at this time. Anesthesia was maintained with epidural anesthesia with 2% lidocaine with epinephrine, inhalation of nitrous oxide, and intermittent intravenous injection of fentanyl. Pancuronium was injected intravenously to maintain muscle paralysis and facilitate controlled mechanical ventilation. Median sternotomy and right-sided thoracotomy was performed in the supine position. The right middle lobe was compressed totally by the tumor, whereas the right upper lobe was expanding normally with ventilation. The tracheal lumen of the double-lumen tube was disconnected from the anesthesia machine to provide access to air and only the left lung was ventilated with 50% nitrous oxide and 50% oxygen during the procedure of tumor resection. During this period analysis of arterial blood gases remained within normal range (pHa of 7.44, arterial O_2 tension of 168 mm Hg, and arterial CO_2 tension of 34 mm Hg).

Removal of the mediastinal tumor was completed uneventfully 2 h later. Analysis of arterial blood gases revealed the following values: pHa 7.38, arterial O_2 tension 189 mm Hg, and arterial CO_2 tension 39 mm Hg with fraction of inspired O_2 0.5. The weight of the tumor was 1030 g. The right lung was deflated for 2 h during tumor removal. Before closure of the thorax, reinflation of the right lung was required to check air leakage and both lungs were expanded with manual positive-pressure ventilation with 20 cm H_2O of peak inspiratory pressure. Hemo-

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Address correspondence to Dr. Matsumiya, Department of Anesthesia, Tsuchiura Kyodo Hospital, Tsuchiura City, Ibaraki 300, Japan.

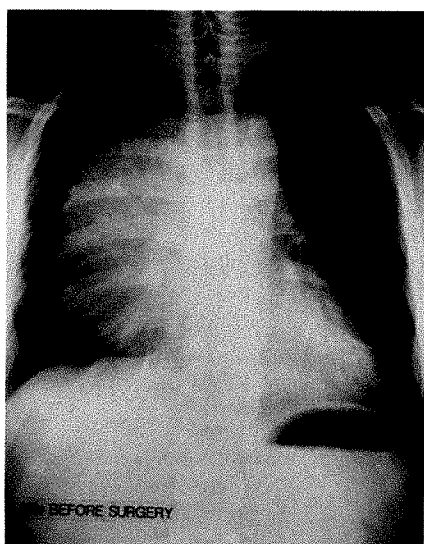


Figure 1. Chest roentgenogram showing large mediastinal tumor 1 mo before surgery.

dynamic responses to lung inflation were not remarkable (systolic arterial blood pressure 140–144 mm Hg, heart rate 102–98 beats/min). Central venous pressure was 7 mm Hg. Small amounts of sputum were aspirated from the right bronchus 30 min later. Thereafter, gasping respiration developed. Immediately after the completion of surgery, copious amounts of frothy pulmonary edema fluid flowed from the right bronchus. A sample of the fluid showed the total protein content to be 3.2 g/dL, with a pulmonary edema-serum protein ratio of 0.71, demonstrating increased pulmonary vascular permeability. No frothy fluid was aspirated from the left bronchus. Analysis of arterial blood gas data revealed the following values: pHa 7.37, arterial O_2 tension 373 mm Hg, and arterial CO_2 tension 41 mm Hg with fraction of inspired O_2 1.0. A chest roentgenogram showed diffuse alveolar infiltrates over the right lung field with clear left lung field (Figure 2). The blood loss was 3500 mL during the operation, which lasted for 5 h, and the patient received 4400 mL of crystalloid, 1000 mL of colloid, and 2000 mL of whole blood intravenously. The endobronchial tube was replaced by an endotracheal tube, and the patient was transferred to the intensive care unit where he was treated with controlled mechanical ventilation with 5 cm H_2O of peak end-expiratory pressure. Epidural injection of 6 mL of 0.25% bupivacaine and 5 mg of morphine through the epidural catheter provided analgesia. Midazolam was administered for sedation. The aspiration of frothy edema fluid was continued and endotracheal suctioning every 30 min was required. Thereafter systolic arterial blood pressure gradually decreased to 80 mm Hg. With rapid transfusion of

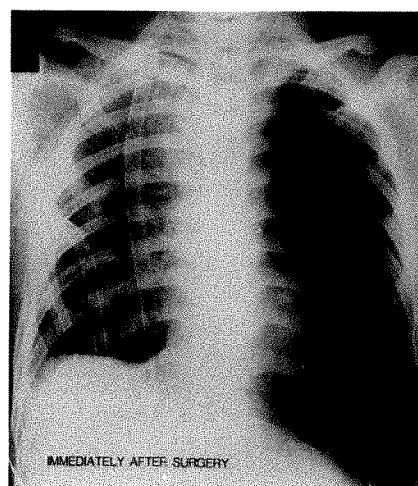


Figure 2. Chest roentgenogram immediately after the surgery showing unilateral pulmonary edema.

colloid, arterial blood pressure returned to normal. Ten hours later, his condition improved markedly and continuous positive airway pressure was started instead of controlled mechanical ventilation. Over the next 30 h, hemodynamic and respiratory status was stabilized. The trachea was extubated on the following day. Serial chest roentgenograms showed that the pulmonary edema was resolving during the following 3 days. The remainder of his time in the intensive care unit was uneventful.

Discussion

This is an unusual case of RPE that developed immediately after the surgical extirpation of an anterior mediastinal tumor during contralateral one-lung ventilation anesthesia.

Many factors are associated with the development of RPE. The duration and severity of the lung collapse and the speed of reexpansion are important (1). The duration of lung compression by the mediastinal tumor in this case was more than 80 days before surgery, whereas the duration of lung atelectasis of the right middle lobe was about 20 days. The chest roentgenogram obtained the day before the operation revealed enlargement of the mediastinal tumor to occupy the lower half of the right lung field, and bronchoscopic examination just after endobronchial intubation revealed narrowing of the right main bronchus. Complete collapse of the lung is one risk factor of RPE. This is substantiated by the report that described RPE localized to one lobe that collapsed completely due to pneumothorax, and partially collapsed lobes that did not develop RPE after reexpansion (4). In our case, although a complete airless area was confined to the right middle lobe and the lower

lobe was partially collapsed, RPE developed in the right lung as showed in Figure 2. Therefore, the complete collapse of the lobe because of compression by the mediastinal tumor was not the sole cause of the development of RPE in our case. Thus, we speculate that complete collapse of the right lung might contribute to the development of RPE. We used one-lung ventilation to avoid the interruption of surgical manipulation owing to lung inflation. Recently, a more acute form of RPE after only 2 h of atelectasis during the thoracic stage of esophagectomy (5) has been reported. Furthermore, one instance of unilateral pulmonary edema after rapid reexpansion of an atelectatic lung of short duration due to accidental placement of the endotracheal tube in the right mainstem bronchus was reported (2). Therefore we cannot exclude the possibility that a 2-h collapse of the right lung during one-lung ventilation could contribute to the development of RPE in our case.

Most clinical and experimental observations support increased pulmonary vascular permeability as a major factor in the development of RPE (6-8). Possible mechanisms of the increase in pulmonary vascular permeability include anoxic damage to the capillary endothelium and mechanical damage to the blood vessel from overstretching during the process of reexpansion (1,8). Furthermore, a recent study demonstrated a potential role for free radicals provided by neutrophils in the increase in pulmonary vascular permeability as a cause of RPE (9,10). Free radicals mediate damage in a variety of pathological conditions including ischemia in organs such as myocardium, intestine, and brain (11,12). Reoxygenation of ischemic tissue results in tissue damage (13). One potential mechanism of this reperfusion injury is that oxygen radicals lead to lipid peroxidation and membrane injury. Thus, one-lung ventilation of unilateral lung followed by bilateral lung ventilation may cause ischemia and reperfusion injury in the nonventilated lung and may increase pulmonary vascular permeability.

We used cervical epidural anesthesia in addition to light general anesthesia in the present case. Although cervical epidural anesthesia has the possibility of causing cardiovascular changes, thoracic sympathetic blockade created by it using lidocaine is unlikely to affect pulmonary hemodynamics modifying the severity of pulmonary edema. Rather, thoracic epidural

anesthesia could minimize the deterioration in pulmonary oxygenation after oleic acid-induced pulmonary edema in sheep (14). But the effects of this anesthetic technique on pulmonary vascular permeability are unknown.

We demonstrated a case of RPE in which collapse of the unilateral lung due to one-lung ventilation and manual reinflation of the collapsed lung were significant factors in its development. The result is often nothing more than a roentgenogram diagnosis of patchy consolidation and usually little or no clinical consequence. However, we should be aware that the institution of one-lung ventilation may cause an increase in pulmonary vascular permeability at the time of bilateral lung ventilation.

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Changes in Somatosensory Evoked Responses During Carotid Endarterectomy Related to Head Position

P. E. Gautier, MD, P. L. Baele, MD, J. M. Guerit, MD, PhD, and Y. Kestens-Servaye, MD

Departments of Anesthesiology and Clinical Neurophysiology, Saint-Luc Hospital, Louvain-Medical School, Brussels, Belgium

Monitoring of cerebral function during carotid endarterectomy probably attenuates the risk of brain damage (1–3). Occlusion of the carotid artery, cerebral embolization of material or air, and hypotension can alter the electroencephalogram or the somatosensory evoked potential (SEP) (4–6). We report SEP changes related to head position and a hypotensive episode in the same patient.

Case Report

A 68-yr-old, 70-kg man with diffuse arteriosclerotic disease was referred for left carotid artery surgery 4 wk after a transient ischemic attack. High arterial blood pressure was controlled with lisinopril, 5 mg twice daily. The patient's medical history showed no angina or myocardial infarction. Preoperative neurologic assessment included SEP and clinical examination. Particular attention was given to the patient's head motion range. Lisinopril was continued during the day of surgery and 0.5 mg of atropine was given intramuscularly 1 h before induction of anesthesia. Monitoring included pulse oximetry, a five-lead electrocardiogram with ST segment analysis, a radial artery catheter, and capnography. Anesthesia was intravenously induced with 3 $\mu\text{g}/\text{kg}$ of fentanyl, 4 mg/kg of thiopental, and 0.4 mg/kg of atracurium. After tracheal intubation, blood pressure increased from 130/68 to 210/110 mm Hg. Trinitrate isosorbide (1 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) controlled the hypertension. Anesthesia was maintained with 0.4%–0.6% isoflurane and intravenous fentanyl boluses (total = 150 μg) with normocarbia.

The monitoring of SEPs was installed after induction of anesthesia. Recording modalities are summarized in Table 1. Somatosensory evoked potentials after induction were similar to those recorded 2 days

before induction (Figure 1a). The patient's head was then positioned for the operation, extending the neck and rotating the head to the right. Within 8 min, the SEPs showed a dramatic decrease in amplitude of both the late P45 parietal component and the prerolandic N30 and a 1.2-ms increase of the CCT, without comparable changes in N13 amplitude (Figure 1b). Examination of trend curves (Figure 2) also shows a slight reduction of the parietal N20 amplitude. This was interpreted as reflecting ischemia in the left sylvian territory and prompted the anesthesiologist to place the head in its neutral position. This led to full SEP recovery after 8 min (Figures 1c, 2).

During surgical dissection, despite stable conditions of anesthesia, the heart rate suddenly decreased from 100 to 80 beats/min and arterial blood pressure, from 140/70 to 110/65 mm Hg. This led to new dramatic SEP alterations consisting of both the P45 parietal component and the prerolandic N30 and a 1.8-ms increase of the central conduction time (with respect to the postinduction values, the parietal N20 amplitude was also slightly decreased) (Figure 1b). The cervical N13 amplitude was unchanged. The carotid body was infiltrated with 10 mL of 2% lidocaine, dopamine (5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), and 300 mL of colloids were administered intravenously over 5 min. Somatosensory evoked potentials regained the postinduction baseline once systolic blood pressure increased above 150 mm Hg (Figure 1e). Because of position and blood pressure changes, a shunt was used independent of the response of SEPs to carotid artery clamping. Neurophysiologically, the rest of the operation proceeded uneventfully. In particular, no changes linked to carotid artery clamping and shunting were observed. The patient woke up without neurologic deficit.

Discussion

Three criteria should be met in order for a given surgical electrophysiologic monitoring to be useful: (a) adequacy, the neural structures tested by electro-

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Address correspondence to Dr. Baele, Service d'Anesthesiologie, Cliniques Universitaires Saint Luc, Avenue Hippocrate, 10/1821, 1200 Bruxelles, Belgique.

Table 1. Somatosensory Evoked Potential Recording Modalities

Channel	Active electrode ^a	Peaks analyzed	Generators
1	C-4 spinous process	N13	Dorsal cervical H
2	C ^b	P14 N20-P27-P45	Medulla (lemniscus) parietal cortex
3	C4 ^b	P14	Medulla (lemniscus)
4	Fpz	P14 P22-N30	Medulla (lemniscus) frontal cortex

^aCommon reference: linked earlobes.^bElectrode is 2 cm behind Cz (10-20 International System), 7 cm laterally.

physiologic monitoring must be those at risk during operation; (b) sensitivity of the electrophysiologic monitoring to the pathophysiologic process involved; (c) possible surgical riposte to any detected incident. Somatosensory evoked potentials test nervous structures depending on both the vertebrobasilar trunk (the lemniscal P14) and carotid arteries (all cortical activities). As regards the second criterion, the sensitivity of SEPs to nervous ischemia has been widely documented (7-9).

The main goal of SEP recording is the detection of brain ischemia after carotid artery clamping. Somatosensory evoked potentials seem more sensitive than the measurement of stump pressure (10) or the electroencephalographic recording (11,12), and their

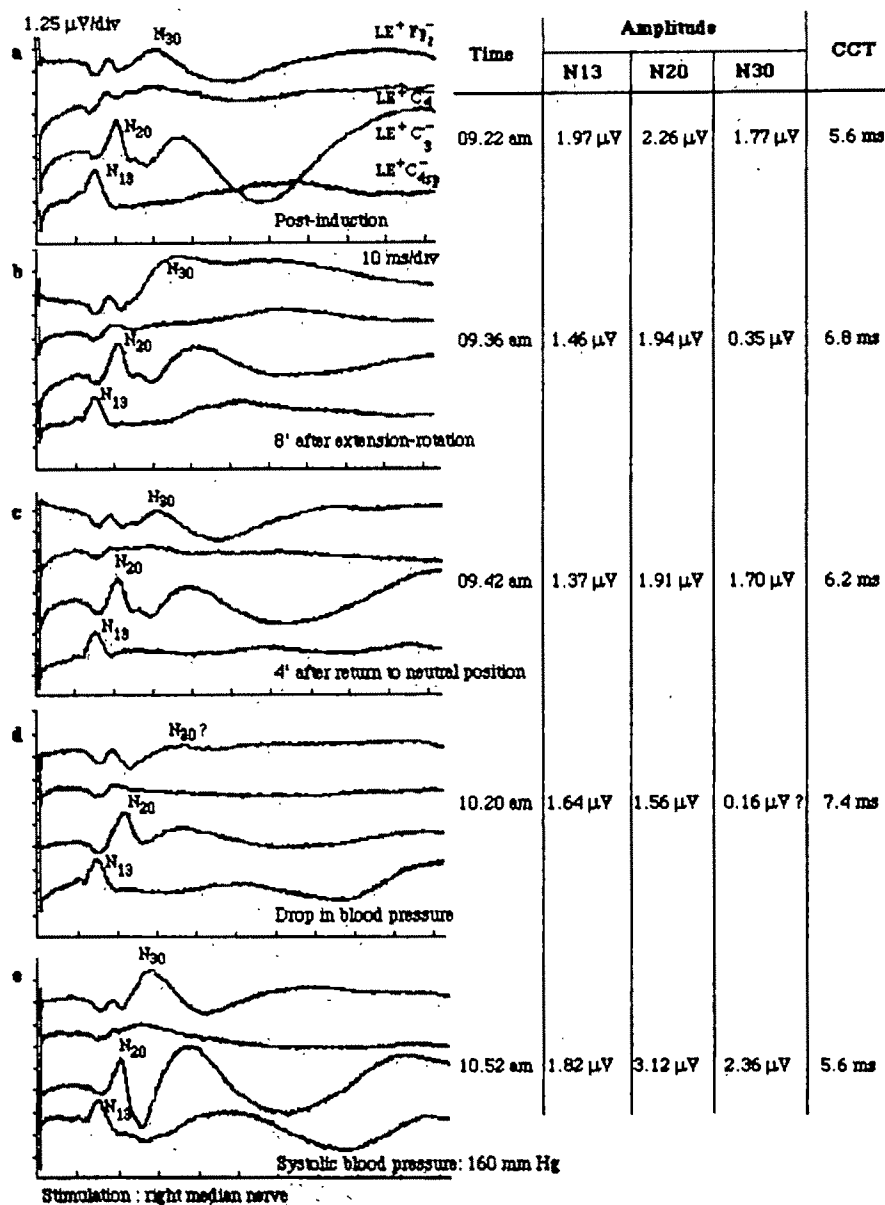


Figure 1. Somatosensory evoked potentials recorded after induction (a), 8 min after head positioning (b), 4 min after return to neutral position (c), during the relative hypotension (d), and after return to higher blood pressure (e). LE, linked ears (reference). A negativity at the active electrode is represented as an upward deflection.

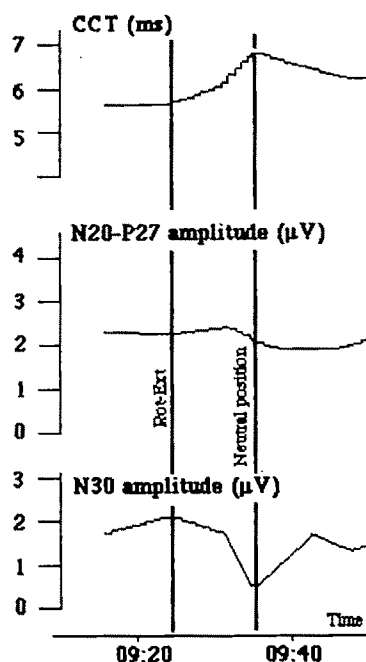


Figure 2. Trend curves of CCT, N20-P27 amplitude, and N30 amplitude. Rotation-extension of the head gives rise to a dramatic decrease in N30 amplitude, a slight decrease in N20 amplitude, and a 1.2-ms increase in the CCT.

alterations should prompt the surgeon to shunt the excluded carotid artery segment. A 1-ms increase in the CCT and a 50% decrease in N20-P27 amplitude are classically considered as indications to shunt. In our experience, as in that of De Scisciolo (13), decreasing amplitudes of the late parietal and frontal components could constitute a more sensitive criterion of ischemia. In any case, an adequate riposte can be provided by the surgeon, which fills the third criterion when brain ischemia is induced by carotid artery clamping.

Our case report illustrates two further applications of SEP monitoring in carotid endarterectomy: to monitor the influence of systemic blood pressure and that of head position. Several cases of SEP alterations secondary to systemic hypotension have been described (4). However, SEP deterioration has only been reported once after changing the position of a patient's head, involving a totally different mechanism (14). In that case, cortical activities disappeared, but cervical waves were preserved after flexion and leftward rotation of the head for a posterior fossa craniotomy. Frontal cortical activities were not evaluated because a frontal reference for parietal recordings had been chosen. This patient had no reported arterial disease, and SEP changes were probably due to direct pressure on the brainstem with a possible influence of venous engorgement.

In the present case, positioning the head clearly

altered SEPs in a way mimicking changes observed in other patients after clamping. This occurred without modification in depth of anesthesia, hemodynamic variables, oxygenation, or ventilation. The delay (between 5 and 8 min) is also in accordance with that expected from ischemia-induced changes (10). We therefore believe that the observed alterations resulted from reversible mechanical occlusion of one of the severely atheromatous carotid arteries. Two further arguments can be set forward to rule out a possible influence of anesthesia: the rapid return toward normal after head positioning and the fact that we failed to observe any increase in the P22 amplitude; the latter phenomenon was recently described for isoflurane concentrations between 0% and 1% and can easily differentiate the alterations due to ischemia from those due to increase in volatile anesthetic concentrations (15). This emphasizes the importance of recording SEPs before induction to get reliable baseline values.

In conclusion, this case shows the necessity of having preoperative baseline SEP recording. Optimal SEP monitoring should be done continuously and be started as soon as possible. Events as small as passive displacement of the head can have deleterious consequences. Preoperative assessment may fail to detect abnormal tolerance to surgical positioning.

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Regional Hypothermia Affects Somatosensory Evoked Potentials

Paul C. Reynolds, MD, Jill A. Antoine, MD, Joseph Bettencourt, MD, and Timothy W. Starck, MD

Anesthesia and Operative Service, Walter Reed Army Medical Center, Washington, D.C.

A wide variety of influences change the amplitude and latency of intraoperative somatosensory evoked potentials (SSEPs). Intraoperative SSEPs are used to assess surgical and anesthetic impact on the central nervous system. Information gained from these tests must be tempered by an understanding of neuroanatomy and neurophysiology as well as a knowledge of the variety of outside influences that change the sensitivity and specificity of the test (1-3). We present a case of a delayed short-latency SSEP that was easily reversible representing a false-positive result.

Case Report

The case involved a 35-yr-old, 55-kg, ASA physical status III woman who was admitted for a clipping of a 1-cm left internal carotid artery aneurysm. Her medical history and review of systems were significant only for her presenting symptom of blurred vision in July 1990. Physical examination was normal except for findings consistent with optic neuritis. Her complete evaluation included a computed axial tomographic scan and internal carotid artery angiogram. The angiogram revealed an aneurysm located distal to the ophthalmic artery on the left internal carotid artery with a 4-5-mm base. The aneurysm was further described as intradural and above the clinoid process.

Preoperative laboratory values were normal with the exception of a hematocrit of 35%. The patient received no premedication. In the operating room, routine noninvasive monitors were placed. A right radial arterial catheter was inserted. Induction of

anesthesia included sufentanil titrated intravenously to 1 $\mu\text{g}/\text{kg}$ with 6 mg/kg of thiopental. Positive pressure ventilation was established, and paralysis was achieved with 0.2 mg/kg of vecuronium given intravenously. Endotracheal intubation was accomplished without difficulty.

Mayfield tongs were placed for positioning, which required 10°-15° rotation of the head to the right with approximately 10° of flexion. Anesthesia was maintained with isoflurane at concentrations of less than 0.5% end tidal as measured by mass spectrometry in combination with a continuous intravenous infusion of sufentanil at concentrations of 0.25-0.5 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$ as needed. Paralysis was maintained with a continuous infusion of vecuronium. This technique allows for a minimum of alteration of SSEP latencies and amplitudes. Additionally, an unchanged regimen maintained throughout the course of the surgery minimized changes of the evoked potentials attributable to anesthetics.

Electroencephalogram and median nerve somatosensory evoked potentials were established and monitored throughout the case. A Nomad system (Tracor Northern, Middleton, Wis.) was used. Evoked potentials were obtained subcutaneously at the C6-7 interspace as well as at C-3' and C-4', all referenced to Fpz. A 200-ms square wave of 20-mA stimulus was applied through intradermal needles at the flexor crease of the wrists lateral to the tendon of the palmaris longus. The low-frequency filter was set at 30 Hz and the high-frequency filter was established at 1500 Hz. A 60-Hz notch filter was also used. A total of 128 sweeps were conducted and the resultant evoked potential signals obtained were averaged. The initial median nerve somatosensory evoked potential tracings are shown (Figure 1) and were obtained at approximately 90 min after induction. The side-to-side difference in latency of the N₀ (first negative deflection recorded at the cervical region) was noted and no intervention was taken. The position was verified by both anesthesiologist and neurosurgeon as not appearing to compromise neural func-

The opinions expressed by the authors are their own. They are not meant to reflect the views of the Department of the Army or of Walter Reed Army Medical Center.

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Address correspondence to Dr. Reynolds, Anesthesia and Operative Service, Department of Surgery, Walter Reed Army Medical Center, Washington D.C. 20307-5001.

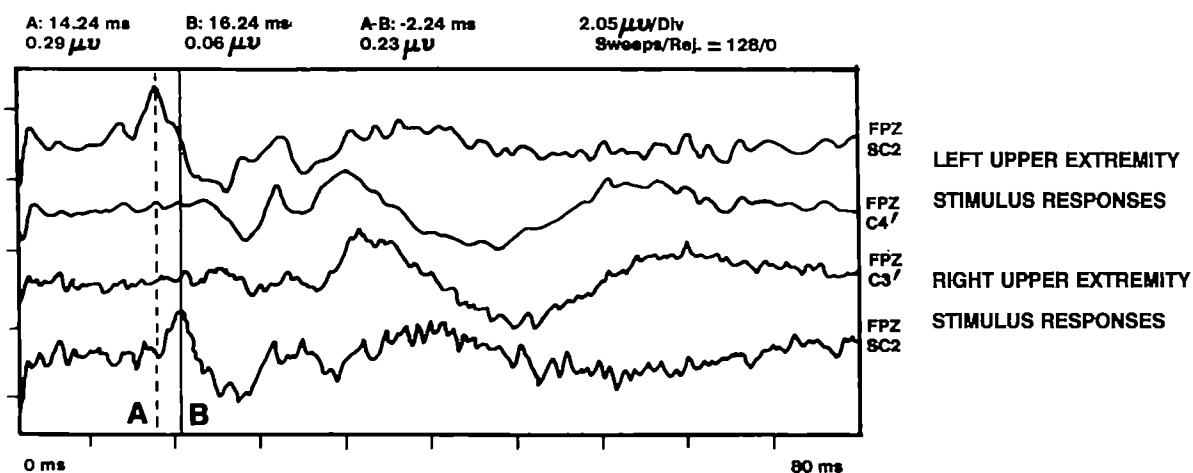


Figure 1. Right and left upper extremity stimulus responses. N_0 is identified by lines A and B. FPZ, C3', and C4' recording electrode sites are as described by Nuwer (reference 11). The SC2 recording electrode site is our designation for the cervical electrode placed in this patient posteriorly at the C4-5 interspace. The initial recordings document a mild side-to-side latency delay. The right-sided evoked potentials recorded in the cervical region are 2 ms later than the left. The central conduction time (not identified in the figure) is not different comparing left to right sides.

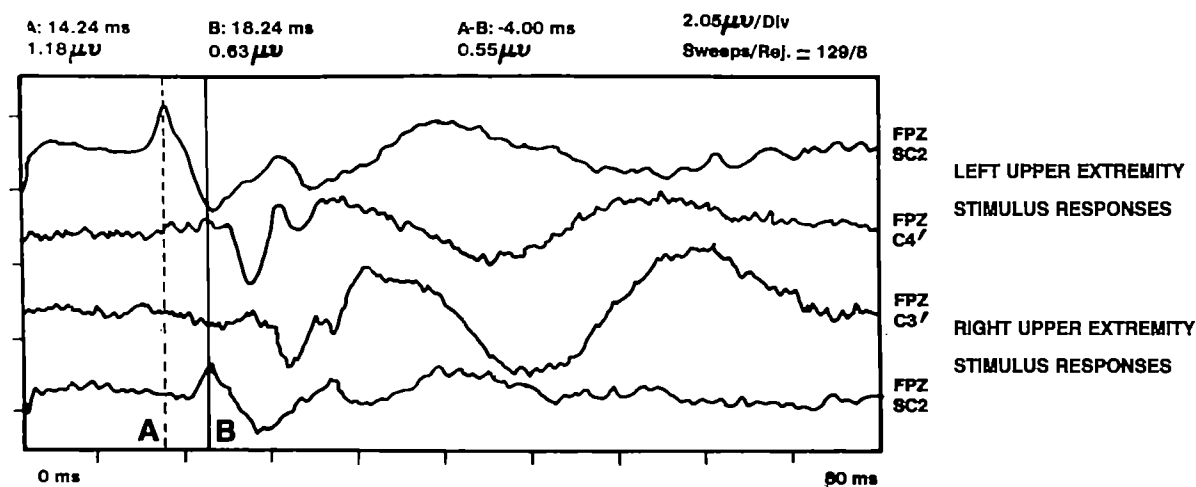


Figure 2. Left and right upper extremity stimulus responses. N_0 is identified by lines A and B. As with Figure 1 the central conduction time is unchanged; however, the latency difference for N_0 from right side to left side has increased to 4 ms.

tion with external compression or excessive flexion/extension. The central conduction time as measured from N_0 to the first negative deflection (N_1) registered at the contralateral cortex was similar for each side.

Approximately 5.5 h into the case, the latency of N_0 had increased by (10%) 1.76 ms (Figure 2). The central conduction time ($N_0 - N_1$) did not appear to have increased. The anesthetic technique chosen had remained stable; end-tidal isoflurane concentrations were 0.3% and remained unchanged for approximately 3 h; the sufentanil infusion had been decreased after craniotomy to $0.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ and had remained so for approximately 3 h. The position had not changed and no external compression of the upper extremity or axilla was noted. The patient remained hemodynamically stable throughout the

case. Her body temperature as measured by esophageal temperature probe was 35.4°C and had not varied by more than $\pm 0.3^\circ\text{C}$. The patient had received cefazolin, mannitol, and decadron during the preceding hours of anesthetic care.

At this time it was noted that the right upper extremity, which had remained exposed during the operation, was cool to the touch. The skin temperature of the volar aspect of the forearm was measured with an infrared scanning thermometer, First Temp model 2000A (Intelligent Medical Systems, Carlsbad, Calif.) and found to be 25°C . The extremity was warmed with heating lamps for approximately 1 h to a skin temperature of 30°C as measured at the same area of the forearm. The N_0 resumed its original location with approximately 2.4 ms of difference

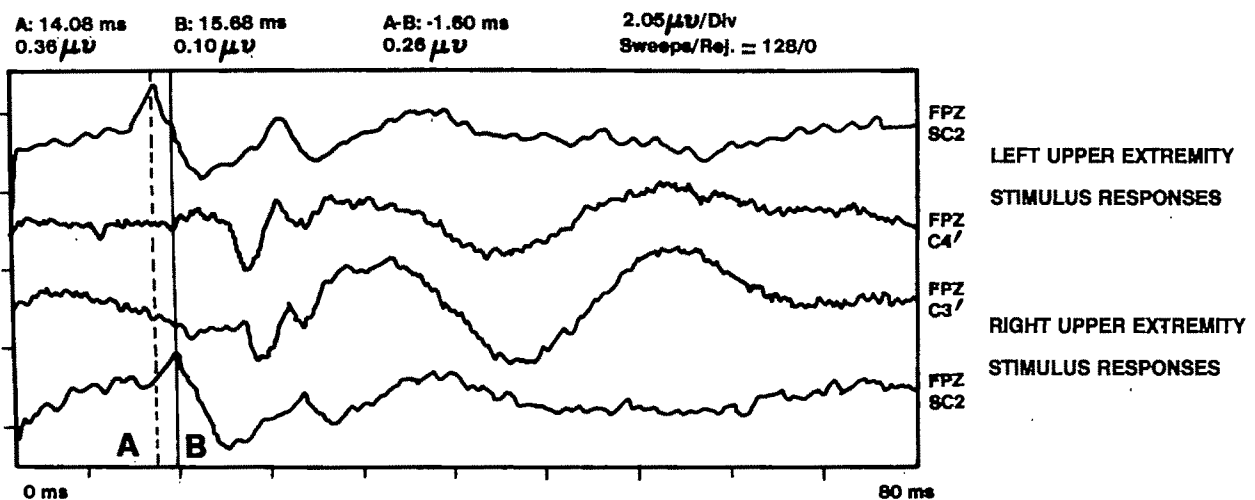


Figure 3. Left and right upper extremity stimulus responses. N_0 is identified by lines A and B. The central conduction time is unchanged. The latency difference for N_0 from right side to left side has decreased to 1.6 ms. Warming of the right upper extremity with radiant warmers had affected the reduction in latency.

comparing left to right side (Figure 3). The contralateral arm was tucked at the patient's side during the case. At the conclusion of the case, a surface temperature of 32°C was obtained at a site similar to that of the exposed arm. After emergence from anesthesia and tracheal extubation, the patient appeared to have suffered no compromise of her central or peripheral nervous systems on physical examination. The patient's internal carotid aneurysm was successfully and uneventfully clipped approximately 35 min after N_0 had reached its maximal latency point.

Discussion

Many authors have described the effects of hypothermia on the latencies of SSEPs (4-8). Some have arrived at formulas to predict this effect. Russ et al. (9) concluded that a linear correlation between latency and tympanic temperature exists in the temperature range of 25°-35°C. Kopf et al. (10) concluded that central conduction time varied as a logarithmic function of the temperature. Budnick et al. (8) described in the rat model a greater hypothermic effect on synaptic transmission than conduction velocity. Most authors concur that hypothermia decreases conduction velocity as well as delays synaptic transmission. Nuwer (3) has indicated in his text that:

It is common for patients in the operating room to drop their core temperature one degree or more over the course of an operation. Limb temperature will often drop several degrees. As is well known in the EMG lab, this can result in a decrease in conduction velocity and an increase in the latency to peaks.

We are unable to use the formulas arrived at by other researchers to help explain the extent of the latency delay seen in our case of regional hypothermia. The formulas derived pertain to hypothermia induced with bypass technology. Possibly an uneven temperature reduction along the course of the peripheral nerves involved in this case could explain the lack of concordance with these studies.

We do believe that reporting of this type of impact on SSEPs may assist others using intraoperative evoked potentials to identify another nonoperative influence. In the present case, the delayed N_0 response was approaching the point at which it could be characterized as a significant change (1,2,4). We chose to reverse the regional hypothermia as other causes of the increased latency seemed less probable. Clearly, the unrelated increased latency was reversible when the limb was rewarmed to a more normal temperature.

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Pressure Sores as a Possible Complication of Epidural Analgesia

Cees D. Punt, MD, Pierre A. F. A. van Neer, MD, and Simon de Lange, MD, PhD

Departments of Anesthesiology and Dermatology, Academic Hospital Maastricht, Maastricht, The Netherlands

Several complications caused by epidural analgesia have been described. Some of these (e.g., cardiac arrest, convulsions, total spinal blockade, and hypotension) occur within minutes, whereas other complications (like epidural hematoma and meningeal infection) become apparent much later (1,2). We describe a complication that occurred in two patients and was discovered 24 h after the start of epidural analgesia.

Case Reports

Patient 1 was a 37-yr-old, otherwise healthy, woman with carcinoma of the cervix who was scheduled for a Wertheim's hysterectomy.

Anesthesia consisted of a combination of general anesthesia and epidural analgesia. A lumbar epidural catheter was inserted and, after a test dose was given, 18 mL of 0.5% bupivacaine with 1:200,000 epinephrine was injected. Immediately thereafter general anesthesia was induced with the intravenous administration of thiopental, fentanyl, and pancuronium. After intubation of the trachea, the patient's lungs were ventilated with 60% nitrous oxide in oxygen. Anesthesia was maintained with isoflurane, and paralysis with pancuronium.

Fifteen minutes after the first epidural bolus injection, at the beginning of the operation, an epidural infusion of 0.25% bupivacaine with 0.25 mg/mL of nicomorphine was started at a rate of 6 mL/h. Throughout the operation the patient lay in the supine position on a thick flannel undersheet and wore long cotton stockings. After induction of general anesthesia, systolic arterial blood pressure decreased from 110 to 90 mm Hg for 10 min and thereafter returned to the preanesthetic level and remained stable throughout the 5-h operation. Nasopharyngeal temperature did not decrease below

35°C. At the end of surgery, residual paralysis was reversed with intravenous neostigmine and atropine and, when spontaneous respiration was assessed as adequate, the trachea was extubated.

Postoperatively, the epidural infusion was continued until the morning after surgery with 0.25% bupivacaine containing 0.125 mg/mL of nicomorphine, which was given at a rate of 6 mL/h. Arterial blood pressure was measured every 15 min for the first hour, then hourly. The patient received 170 mL/h of 3.75% glucose in 0.225% saline and remained hemodynamically stable throughout the first postoperative night. Urinary output was 70 mL/h.

The next morning, 24 h after the start of surgery, a large hemorrhagic blister was discovered on both heels. There were no skin lesions on other parts of the body. A dermatologist confirmed the diagnosis of pressure sores. Therapy consisted of removal of the roof of the blisters, local wound treatment, and heel pads. The sores healed uneventfully.

The second patient was a 30-yr-old, otherwise healthy, woman who had previously undergone several urologic procedures for urinary incontinence and was about to undergo a ureterocolostomy.

Anesthesia consisted of a combination of general anesthesia and epidural analgesia. A lumbar epidural catheter was inserted and, after a test dose was given, 18 mL of 0.5% bupivacaine with 1:200,000 epinephrine was injected. Immediately thereafter general anesthesia was induced with the intravenous administration of thiopental, fentanyl, and succinylcholine. After intubation of the trachea, the patient's lungs were ventilated with 60% nitrous oxide in oxygen. Paralysis was maintained with pancuronium. The patient, with both feet in long cotton stockings, lay in the supine position on a thick flannel undersheet. Halfway through the operation, which lasted 4.5 h, another bolus of 15 mL of 0.5% bupivacaine without epinephrine was given. At the end of the procedure residual paralysis was reversed with intravenous neostigmine and atropine and, when spontaneous respiration was assessed as adequate, the trachea was extubated.

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Address correspondence to Dr. Punt, Department of Anesthesiology, Academic Hospital Maastricht, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands.

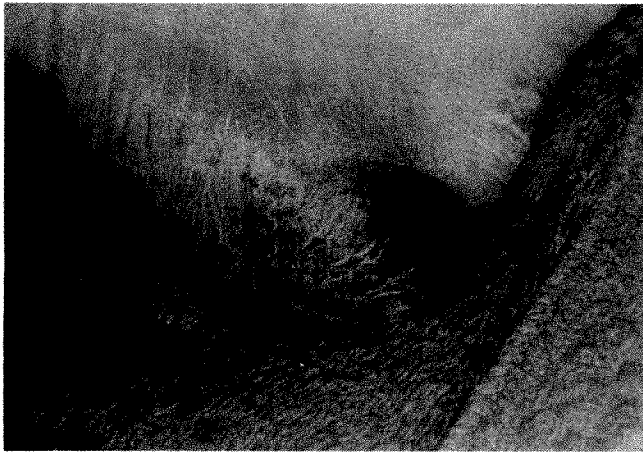


Figure 1. Lateral aspect of the left heel of the second patient showing a large hemorrhagic blister.

Postoperatively, an epidural infusion was started with 0.25% bupivacaine containing 1.25 $\mu\text{g}/\text{mL}$ of sufentanil at a rate of 6 mL/h. Preanesthetic systolic arterial blood pressure was 110 mm Hg. In the first hour of surgery, arterial blood pressure stayed between 80 and 90 mm Hg, and for the remainder of the operation the systolic blood pressure exceeded 90 mm Hg. Postoperatively, systolic blood pressure was between 90 and 105 mm Hg. The patient received 125 mL/h of 3.75% glucose in 0.225% saline and 500 mL of plasma protein solution during the first postoperative night. Urinary output was 95 mL/h. Nasopharyngeal temperature had decreased to 33.8°C at the end of surgery. Three hours after arrival in the recovery room, rectal temperature was 36.0°C.

The morning after surgery, a hemorrhagic blister was discovered on both heels (Figure 1). After removal of the roof of the blisters and local wound treatment, the sores healed uneventfully.

Discussion

The exact mechanism of the development of pressure sores is still not fully understood (3). However, pressure causing local ischemia is probably the fundamental cause (4-6). Other factors, such as shearing force, reduced sensation and mobility, hypotension, peripheral vasoconstriction, vasomotor failure as seen in acute paraplegia, heart failure, dehydration, sepsis, nutritional deficiency, and anemia also play an important role in the pathogenesis of pressure sores (3,4,7-11). Population groups with an increased risk of developing pressure sores are the elderly, the unconscious, the emaciated, the paralyzed, and the bedridden (6,7).

The two patients in this report did not belong to any of these risk groups. They were young and, apart from an overnight fast, their nutritional status was good, they were not dehydrated, they were not anemic, and they were not bedridden.

Hypotension aggravates pressure effects on body surfaces, which may result in ischemic lesions (12). However, in these two patients, the decrease in systolic arterial blood pressure occurring after anesthetic induction was moderate, with a maximum decrease to 80 mm Hg (which occurred for less than 1 h in the second patient).

In a geriatric population, the number of spontaneous body movements during the night is inversely related to the incidence of pressure sores (5). In the supine position, the skin pressure at the sacrum and at the heels exceeds the average capillary perfusion pressure in the skin (13). Bromage (14) states that motor blockade caused by 0.25% bupivacaine is negligible. Therefore, paresis of the legs would not explain the lesion in these two patients. Moreover, one of the patients stated that she had been able to move her legs on the evening of the operative day. However, postoperative somnolence, caused by the general anesthesia (12), and the lack of sensation, caused by the epidural administration of bupivacaine in combination with an opioid, may have inhibited spontaneous patient movement. This may be compared to paraplegics who get no sensory warning of impending ischemia (4,8,10-12).

Superficial sores, like the blisters in these two patients, are often caused by shearing stress (9). This shearing or friction can be caused by sliding down the bed or being pulled up the bed instead of being lifted (4). In this situation lesions of the sacral skin would also be expected (11).

The epidural administration of a local anesthetic causes vasodilation which, owing to pressure, may cause local shunting. This shunting could have resulted in skin ischemia and eventually in pressure sores. This is similar to the vasomotor paralysis in the acute phase of paraplegia, which in a very short time can lead to ischemia caused by local pressure (8,10). If indeed this was a valid explanation, these lesions would be seen more often.

In conclusion, it is not clear which factors are responsible for this complication. Probably the sum of analgesia, postoperative somnolence, possibly slight paresis, and vasomotor paralysis together with a long stay on the operating table resulted in the occurrence of pressure sores. Preventive measures should be initiated early, especially when epidural analgesia is combined with general anesthesia. Nursing management, such as the use of underlying sheepskins, heel pads, and pressure-relieving mattresses and turning the patient at regular intervals

(which is facilitated by the epidural analgesia), is of primary importance in preventing these lesions (3,4,7,9,10,12,13).

We thank Dr. P. Roekaerts for his agreement to use the data of one of the patients.

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Retrograde-Assisted Fiberoptic Tracheal Intubation in Children With Difficult Airways

Steve M. Audenaert, MD, Christopher L. Montgomery, MD, Bart Stone, MD, Robert E. Akins, CRNA, RRT, and Richard L. Lock, MD

Department of Anesthesiology, University of Kentucky Medical Center and Shriners Hospital for Crippled Children, Lexington, Kentucky

A variety of approaches have been described for the clinical management of difficult pediatric airways including retrograde (1,2) and flexible fiberoptic (3) techniques. Use of fiberoptic laryngoscopes (4) and of light wand devices (5) has also been reported. Fiberoptic tracheal intubation over a retrograde wire has been described in adults (6,7) and Stiles has described a two-step bronchoscope and antegrade wire technique in children (8). Small-diameter flexible fiberoptic bronchoscopes have now become available, making use of more "routine" flexible fiberoptic techniques possible even in small newborns. Some of these scopes include a lumen for suction, irrigation, insufflation, and/or passage of a wire. We have now used retrograde-assisted fiberoptic intubation in 20 pediatric patients with difficult airways, including seven children less than 16 mo of age (see Table 1 which gives details concerning cases 1-20). With approval of our institutional human investigations committee, we reviewed our experience. The technique was successful on all occasions, even in instances where other methods mentioned above had failed.

Case Reports

Case 6 and Technique

An 11-mo-old, 7.8-kg male patient with mandibular hypoplasia and Klippel-Feil anomaly was admitted for elective surgery. Rectal methohexital was given to initiate general anesthesia. Intravenous access was established and 0.16 mg of glycopyrrolate was given. Anesthesia was deepened with incremental halo-

thane in oxygen via a Patil-Syracuse mask (Anesthesia Associates, San Diego, Calif.). Spontaneous ventilation was maintained. The airway was secured by the method outlined below.

1. Needle cricothyrotomy was performed using a 22-gauge Teflon catheter over needle. The needle and catheter were advanced in the midline with a 45° cephalad angle until free aspiration of air occurred. The 1-in flexible catheter was then advanced and left in place and the needle was withdrawn.
2. A 100-cm-long, 0.018-in-diameter Teflon-coated guidewire (Cook Critical Care, Bloomington, Ind.) was passed through the catheter and cephalad, spontaneously exiting through the left nostril.
3. The cephalad end of the wire was fed through the suction port of a 2.8-mm-outer-diameter intubating bronchoscope (AUR-8, Circon ACMI, Stamford, Conn.) and secured. A softened, lubricated 4.0-mm-internal-diameter (ID) endotracheal tube had previously been loaded onto the bronchoscope.
4. Phenylephrine (0.25%) was applied to the nasal mucosa. The bronchoscope was fed along the wire until the vocal cords were identified.
5. The bronchoscope was advanced past the vocal cords and the wire was withdrawn.
6. The bronchoscope was then further advanced, and the endotracheal tube was placed to an appropriate depth.

Case 13

A 7-yr-old, 17-kg boy with spondyloepiphyseal dysplasia was admitted for fusion of C1-2 subluxation. Although the cervical spine was believed to be stable in extension, a cautious approach to the airway was chosen. After beginning an intravenous infusion, 0.2 mg of glycopyrrolate and small doses of thiopen-

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Address correspondence to Dr. Audenaert, Pediatric Anesthesia, Kosair Children's Hospital, 231 East Chestnut Street, Louisville, KY 40202.

Table 1. Summary of Clinical Approaches to Pediatric Patients With Airways Difficult to Manage Clinically

Case No.	Age	Weight (kg)	Primary/surgical diagnosis	Airway problems	Scope	Tube	Rationale or failed means of tracheal intubation
1	1 day	2.9	Congenital anomalies/omphalocele	Micrognathia, nonvisualization	AUR-8	3.0	A,D
2	6 mo	4.5	Congenital anomalies/bilateral radial club hand	Nonvisualization	AUR-8	3.0	D
3	7 mo	5.7	Amyoplasia/congenital hip dislocation	Micrognathia, nonvisualization, limited mouth opening	AUR-8	4.0	A,D,F*
4	8 mo	6.8	Amyoplasia/clubfoot	Micrognathia, limited mouth opening, nonvisualization	AUR-8	4.0	A,D
5	10 mo	4.9	Pierre Robin/cleft palate	Micrognathia, nonvisualization	AUR-8	3.5	A,D
6	11 mo	7.8	Arthrogryposis/clubfoot	Klippel-Feil, micrognathia	AUR-8	4.0	A
7	15 mo	8.0	Undiagnosed congenital anomalies/congenital hip dislocation	Nonvisualization	AUR-8	4.0	D
8	24 mo	13.2	Hurler's syndrome/bone marrow transplant	Short neck, large tongue, limited neck motion, nonvisualization	AUR-8	4.0	A,D
9	26 mo	11.4	Camptomelic dysplasia/cervical fusion	Cervical spine abnormalities and instability, limited motion of neck, mouth	AUR-8	3.0	A,C
10	3 yr	11.2	Hallerman Streiff/ophthalmologic procedures	Narrowed trachea, micrognathia, malar hypoplasia, microstomia, nonvisualization	AUR-8	4.5	A,D
11	5 yr (6 yr)	15.1 (16.9)	Escobar syndrome (multiple pterygium)/orthopedic and plastic procedures	Klippel Feil, brevicollis, limited mouth, neck motion, nonvisualization	LF-1	5.0	A,D
12	6 yr	11.3	Multiple congenital anomalies/infantile scoliosis	Micrognathia, cervical hemivertebra, limited mouth opening, nonvisualization	LF-1	5.0	H,A D,R,F*
13	7 yr	17.1	Spondyloepiphyseal dysplasia congenita/C1-2 subluxation	C-spine abnormalities	LF-1	5.5	C
14	7 yr (7 yr)	15.9 (17.1)	Schwartz-Jampel syndrome/C2-3 subluxation	Microstomia, limited neck, mouth motion, C-spine abnormalities	LF-1	5.0	A,C
15	9 yr	14	Cerebral palsy/congenital hip dislocation	Nonvisualization	AUR-8	5.5	D
16	12 yr	22	Escobar syndrome (multiple pterygium)/scoliosis	Klippel Feil, brevicollis, limited mouth, neck motion, micrognathia nonvisualization	LF-1	5.5	A,D,L
17	12 yr	15.2	Undiagnosed congenital progressive neuromuscular disease/extreme cervicothoracolumbar fixed lordosis for release and fusion	Extreme fixed cervicothoracic lordosis, micrognathia nonvisualization	AUR-8	5.0	A,D
18	14 yr	51	Juvenile rheumatoid arthritis/joint fusion	Limited motion neck, mouth	LF-1	5.5	H,A
19	15 yr	71	Juvenile rheumatoid arthritis/phalangeal replacements	Limited motion neck, mouth	LF-1	6.0	H,A
20	17 yr	74	Trauma/cervical spine and facial fractures	Facial fractures, in cervical traction, unstable cervical spine	LF-1	7.5	C

Case numbers have been assigned for reference and convenience only. The tracheas of patients 11 and 14 have each been intubated twice with retrograde-assisted fiberoptic technique. Under "airway problems," nonvisualization refers to failure to expose the cords or arytenoid cartilages with direct laryngoscopy. On all occasions where the AUR-8 scope was used, the 22-gauge catheter and 0.018-in wire (see text) were also used. Likewise, where the LF-1 scope was used, the 20-gauge catheter and 0.025-in wire (see text) were used. "Tube" refers to the endotracheal tube's internal diameter in millimeters. The "rationale or failed means of tracheal intubation" column reveals a few patients where this technique was used primarily, usually for cervical spine consideration (C) or when the airway was known to be extremely difficult by history/previous experience (H), or by preoperative assessment (A). Direct laryngoscopy (D), fiberoptic laryngoscopy (F), lightwand (L), and retrograde alone (R) techniques were attempted unsuccessfully where so noted.

*Use of a Bullard rigid fiberoptic laryngoscope afforded an excellent view of the vocal cords, but owing to limited mouth opening the endotracheal tube could not be properly positioned.

tal were given. Spontaneous ventilation was maintained, and anesthesia was deepened with incremental halothane in oxygen via a Patil-Syracuse mask. The airway was then secured using the method already described but with a larger bronchoscope (Olympus LF-1), wire (0.025 in.), catheter (20 gauge), and endotracheal tube (5.5 mm ID).

Case 12

A 6-yr-old, 11.3-kg, 96-cm-tall girl with anomalies including micrognathia and multiple hemivertebra was admitted for posterior fusion of infantile scoliosis. Anesthesia was induced with rectal methohexital and was deepened with incremental halothane in oxygen. Neither direct nor fiberoptic laryngoscopy (Bullard) revealed identifiable laryngeal landmarks, and a small amount of airway bleeding was caused. A retrograde wire was placed and intubation following that guide was attempted, but the tube would not pass the level of the glottis despite rotation of the tube (9,10) and various maneuvers of the wire and larynx. Neuromuscular blockade was established to no avail. The endotracheal tube was removed from the wire and loaded onto the bronchoscope. The cephalad end of the wire was then passed through the bronchoscope and the bronchoscope was advanced. Vision was obscured by blood-tinged secretions but saline lavage and suction allowed visualization of tracheal rings, and the wire was withdrawn. The bronchoscope advanced readily to the distal trachea and intubation with a 5.0-mm-ID tube was easily accomplished.

Case 14

A 7-yr-old, 17-kg boy with Schwartz-Jampel syndrome, severely limited mouth opening, and residual C2-3 subluxation after cervical spine fusion was admitted for cervical spine fusion of additional levels (and at another date for dental procedures). Glycopyrrolate, ketamine, and midazolam were given intravenously. Transtracheal lidocaine and bilateral superior laryngeal nerve blocks were performed. Retrograde-assisted fiberoptic tracheal intubation was performed without incident.

Case 16

A 12-yr-old girl with Escobar (multiple pterygium) syndrome and micrognathia was admitted for extensive orthopedic surgery. Klippel-Feil anomaly and atlanto-occipital abutment were noted on preoperative cervical spine film. Direct laryngoscopy did not provide a view of the larynx, and light wand intuba-

tion (Tube-Stat, Concept, Clearwater, Fla.) was attempted unsuccessfully. Retrograde-assisted fiberoptic tracheal intubation was performed. An anterior larynx, extremely floppy epiglottis, and a very small glottic opening were noted and passed, albeit with considerable difficulty.

Discussion

Retrograde-assisted fiberoptic tracheal intubation can be performed by an anesthesiologist with one assistant. It has distinct advantages compared to isolated retrograde or fiberoptic techniques. Its chief advantage over other retrograde techniques lies in the ability to pass the glottic opening with visual direction. This allows the bronchoscope to pass without hanging up on the arytenoid cartilage or the epiglottis (9,10). Reducing tension on the wire (10,11), use of a slightly smaller than usual endotracheal tube (11), and rotation of the tube (9,11,12) are maneuvers useful in helping the tube to pass smoothly with or without the bronchoscope in place. It has been our observation, however, that the incidence of failure to pass the glottis with blind retrograde techniques is particularly high in children (as in case 12). The presence of the larger, stiffer bronchoscope as a guide (as opposed to a wire or epidural catheter) almost completely eliminates this "hanging up" phenomenon. In only one of our patients was it difficult to pass the glottis.

Another advantage of this technique is that in smaller patients or patients with pulmonary compromise, oxygen insufflation can be used during these manipulations and may help to preserve vision (12) and maintain oxygenation (12,13). We insufflated oxygen prophylactically in our five youngest patients (cases 1-5, 700-1000 mL/min oxygen) and in response to arterial oxygen desaturation to 86% and to 89% in two other patients (cases 12 and 16, 2 and 4 L/min, respectively). None of the five younger patients suffered arterial oxygen desaturation to less than 96%, and oxygen saturation improved in the two patients treated with insufflated oxygen.

Compared with standard fiberoptic techniques, the major advantage of this technique lies in the presence of the guidewire. By following the wire the bronchoscopist can quickly pass through the oropharynx or nasopharynx without taking time to recognize landmarks along the way. This reduces the time necessary to accomplish intubation, especially in difficult cases. Even if landmarks are obscured, simply by following the wire until the bright white Teflon catheter is seen, the bronchoscopist can quickly and easily reach the vocal cords. This speed is most noticeable with an inexperienced bronchoscopist. Practitioners who rarely use a flexible bronchoscope

Table 2. Flow Measurements of Various Fiberscopes

Scope (Mfg)	Outer scope diameter (mm)	Inner lumen diameter (mm)	Working length (cm)	Maximum tip flexion (°)	Scope configuration	Maximum O ₂ flow (L/min)
AUR-8 (Circon ACMI)	2.7	0.8	37	140	Straight	9.4 ± 0.1
					90° curve and 90° tip flexion	9.4 ± 0.0
					90° curve with 0.018-in wire in place	4.37 ± 0.01
LF-1 (Olympus)	3.8	1.2	60	120	Straight	18.1 ± 0.2
					90° curve and 90° tip flexion	17.9 ± 0.1
					90° curve with 0.025-in wire in place	12.4 ± 0.1
BF-1 (Olympus)	5.9	2.8	55	100	Straight	159 ± 5
					90° curve and 90° tip flexion	152 ± 1
					90° curve with 0.035-in wire in place	145 ± 1

Mfg, manufacturer.

Flow measurements represent mean ± sd.

can quickly follow a guidewire to the glottic opening. This transforms an often time-consuming ordeal to a quick and effective maneuver.

This technique, with the equipment described, can be used with endotracheal tubes as small as 3.0-mm ID. It avoids the multiple-step fiberoptic techniques previously recommended for pediatric applications (8,14). No significant complications have occurred in any of the pediatric patients thus far managed by this approach. Although it is a safe and relatively fast technique, it does have limitations. Special equipment is needed, including long, small wires (available in most cardiac catheterization laboratories) and Patil-Syracuse masks or their equivalent. The Patil-Syracuse mask facilitates maintenance of deep levels of general anesthesia and spontaneous ventilation (15), both of which are helpful in pediatric fiberoptic approaches. A pituitary (or endoscopic grasping) forceps is useful for wire retrieval should the wire coil in the posterior pharynx. This is especially true when mouth opening is limited, as that may preclude use of Kelly or Magill forceps. An intubating bronchoscope with a working channel is vital to this technique. This working channel can be used to irrigate with saline solution or local anesthetic or to apply suction. The channel can also be used, as in this report, to follow a wire, to insufflate gas (16), or both. Even with the smaller scope described here, oxygen flow of more than 4 L/min can be maintained with the 0.018-in-diameter wire in place. Maximum oxygen flow through this scope without a wire is more than 9 L/min (see Table 2 for details). Such flows are more than adequate to maintain oxygenation in these smaller patients (17). We have generally limited flow to approximate the patient's normal minute ventilation. This has been clinically successful and avoids excessive gas velocities that might create mechanical

trauma and shear stresses leading to injury of the tracheobronchial tree (18).

Cricothyrotomy and passage of the wire, as well as the actual intubation, was well-tolerated by all our patients. When halothane was used, a level of approximately 2 age-adjusted MAC (19,20) was generally sought and yielded excellent conditions (21). In four patients (cases 9, 14, 18, and 20) these procedures were performed with intravenous sedation and local anesthesia, and in the one newborn following a bolus of intravenous thiopental. Special caution, however, is needed when performing needle cricothyrotomy in small patients. Review of more than 17,000 needle cricothyrotomies in adults revealed no serious complications (22), but no data are available on this procedure in children. Landmarks may be vague and will be more cephalad in younger children. Importantly, the distance from the cricothyroid membrane to the true cords is very small. This distance has been reported as 13 mm in adults (22), but in our smallest patients the distance was less than 5 mm. Care must be taken when puncturing the membrane to limit advance of the needle to the point of free air aspiration. Potential damage to cords or structures posterior to the trachea can thus be avoided. A slight cephalad angle helps the wire to advance in the desired direction, and on the rare instance that it does not appear, it can be withdrawn and readvanced. Leaving the Teflon catheter in place as a sheath helps maintain sterility during any maneuvers of the wire. Final withdrawal of the wire is done in the caudad direction so that any friction between the wire and bronchoscope helps maintain scope position, rather than tends to dislodge it. The Teflon catheter remains in place until proper endotracheal tube placement is confirmed.

In summary, use of the described pediatric flexible

bronchoscopes makes possible "intubation over the scope" with endotracheal tubes as small as 3.0 mm ID. Placing a retrograde wire through these fiberoptic scopes allows even an inexperienced bronchoscopist to quickly follow the wire to the glottic opening. This combination of techniques allows abnormal landmarks, edema, and small amounts of blood to be quickly bypassed. Oxygen insufflation can be performed throughout bronchoscopy and intubation. Although not a routine technique, retrograde-assisted fiberoptic intubation is a valuable addition to our methods of securing a difficult pediatric airway.

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Termination of Supraventricular Tachycardia With Adenosine in a Healthy Child Undergoing Anesthesia

Ronald S. Litman, DO, Thomas P. Keon, MD, and Frederick W. Campbell, MD

Department of Anesthesiology, University of Pennsylvania; Hospital of the University of Pennsylvania; and Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

Cardiac arrhythmias associated with hemodynamic changes are uncommon in healthy children undergoing anesthesia. Sinus bradycardia, junctional rhythm, and occasional premature atrial or ventricular contractions occur commonly but do not cause important changes in systemic arterial pressure. We describe a child in whom paroxysmal supraventricular tachycardia (SVT) and hypotension developed with induction of anesthesia, which was converted to sinus rhythm by administration of adenosine—a relatively new treatment for reentrant SVT.

Case Report

A 7-yr-old, 30-kg girl, ASA physical status I, was admitted for elective tonsillectomy and adenoidectomy because of chronic adenotonsillar enlargement and nighttime snoring. She had a history of one prior general anesthetic without incident.

Atropine (0.5 mg) was given orally approximately 45 min before induction of anesthesia. Sedative premedication was not given because of her history of airway obstruction while sleeping. In the day-surgery holding area, the patient was very anxious and extremely resistant to parental separation. Upon arrival in the operating room, the patient was combative and strongly resisted an attempt at an inhaled induction of anesthesia. Therefore, a 27-gauge butterfly needle was inserted into a vein on the dorsum of the hand. Thiopental (150 mg) and vecuronium (3 mg) were administered intravenously. As the patient lost consciousness, ventilation via bag and mask was begun with 70% nitrous oxide, 30% oxygen, and 2% inspired concentration of halothane before placement of routine monitors. When the precordial stethoscope and electrocardiographic leads were in place, we unexpectedly noted a heart rate of 240 beats/min. The

DINAMAP device was unable to measure an arterial blood pressure but femoral pulses were clearly palpable. The halothane was discontinued. The trachea was intubated, and the lungs were ventilated without difficulty.

The electrocardiographic tracing revealed a narrow complex regular tachycardia without discernible P waves. A diagnosis of paroxysmal SVT was made. Unilateral carotid massage was performed, but the heart rate remained rapid. The DINAMAP read an arterial blood pressure of 60/30 mm Hg. Adenosine (3 mg, 0.1 mg/kg) was given intravenously without effect. Phenylephrine (0.1 mg IV) was then administered and arterial blood pressure increased to 77/35 mm Hg; however, the heart rate remained the same. Approximately 1–2 min later, a second dose of adenosine was given by IV bolus injection at a dose of 6 mg (0.2 mg/kg, double the initial dose). Within 10 s the cardiac rhythm converted to sinus (Figure 1) with a rate of 120 beats/min. The systemic arterial pressure now measured 82/56 mm Hg.

The nurse who was restraining the patient remarked that she had felt the patient's heart "racing" before the patient lost consciousness. The SVT, therefore, may have been present before induction of anesthesia. A 12-lead electrocardiogram and cardiac consultation did not suggest intrinsic cardiac disease, and the surgery proceeded uneventfully. Maintenance anesthesia consisted of nitrous oxide, isoflurane, and 0.15 mg of fentanyl. Postoperatively, the patient remained in sinus rhythm and recovered uneventfully.

Discussion

Pediatric cardiologists report that SVT is the most common arrhythmia noted in the pediatric age group (1). It can occur in utero, at birth, or can be acquired. Predisposing conditions include infection, drug exposure, Wolff-Parkinson-White syndrome, and various forms of congenital heart disease. In this patient, SVT may have begun before induction of anesthesia,

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Address correspondence to Dr. Litman, Department of Anesthesiology, Strong Memorial Hospital, 601 Elmwood Avenue, Rochester, NY 14642.

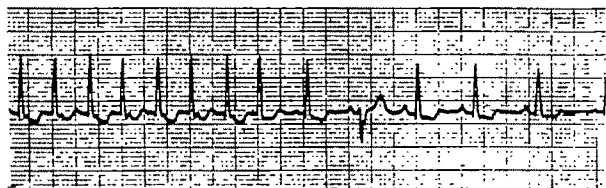


Figure 1. Supraventricular tachycardia at a rate of 240 beats/min is converted to normal sinus rhythm at a rate of 120 beats/min after IV administration of 0.2 mg/kg adenosine.

based on the nurse's description of her fast heart rate. This may have been caused by excessive sympathetic activity precipitated by fear and anxiety associated with parental separation and surgery. Oral atropine 45 min before induction of anesthesia may have been a contributing factor.

Adenosine, an endogenous purine nucleoside normally found in all human tissues, expresses its primary electrophysiologic action as transient depression of atrioventricular conduction, with resultant termination of SVTs which depend on a reentrant circuit involving the atrioventricular node (2). In adults, adenosine proved effective in terminating 94% of episodes of SVT in 25 patients in one series (3) and all 20 episodes in another study (4).

Several recent investigators have suggested that it may be the drug of choice in terminating SVT in infants and children (5-7). An initial bolus injection of 0.05 mg/kg is suggested, with doubling of the dose until either a desired effect is attained or a maximum of 0.2 mg/kg is administered. Clarke et al. (6) reported on the use of adenosine in terminating chronic refractory SVT in three infants, aged 7-44 days, and one 10-yr-old child. Supraventricular tachycardia was terminated in all patients within 20 s after administration of adenosine with doses of 0.1-0.25 mg/kg IV. The only side effect reported was transient bradycardia to 40 beats/min in a 28-day-old infant that spontaneously subsided after 40 s. In 13 patients with SVT, aged 1 day to 16 yr, the arrhythmia was terminated with adenosine using dosages from 0.0375 to 0.225 mg/kg without side effects (7).

Adverse effects that have been reported with the use of adenosine include dyspnea, facial flushing, and chest pain, all of which subsided in a few minutes. Because of its metabolism by circulating adenosine deaminase and rapid transport into cells, the drug disappears from the circulation almost immediately, and thus has an extremely short half-life of several seconds. Side effects, therefore, are short-lived. Heart block and bradycardia may occur after adenosine's termination of the SVT but tend to occur only when using exceptionally large doses and are transient in nature.

The administration of phenylephrine may have

contributed to the termination of this patient's SVT but we believe that this is unlikely. In one report (8), phenylephrine was used to terminate SVT in 10 patients. The authors observed that the increase in arterial blood pressure caused by phenylephrine caused an initial slow decline in the rapid heart rate before conversion to sinus rhythm. They therefore proposed that this increase in blood pressure caused baroreceptor stimulation with resulting increased reflex vagal activity. The patient we describe had a substantial increase in blood pressure in response to phenylephrine, but without a decrease in heart rate before the rhythm converted to sinus after the administration of adenosine. Furthermore, the lack of a primary role of phenylephrine in the termination of the SVT is suggested by the failure of another vagotonic maneuver, carotid sinus massage, to change the rhythm or alter the heart rate.

There also exists the possibility that the patient had spontaneous conversion from SVT to sinus rhythm that was unrelated to any of the drugs administered. However, as there is such a distinct temporal association with the administration of adenosine, we believe that spontaneous conversion is unlikely.

A case similar to this was reported by Chow and Noble-Jamieson (9) in which adenosine was administered to terminate SVT in a 6-yr-old girl undergoing tonsillectomy and adenoidectomy. They used 0.05 mg/kg and within 20 s had converted her rhythm to sinus tachycardia with a rate of 150 beats/min. Whereas doses up to and including 0.2 mg/kg have been used safely in awake adults and children, this is the first report of the safe use of this dose in an anesthetized child.

In conclusion, we report the use of adenosine in a dose of 0.2 mg/kg to terminate an episode of paroxysmal SVT in a healthy child under anesthesia. Adenosine appears to be a safe and effective drug for the treatment of paroxysmal supraventricular tachycardia in anesthetized children.

We thank Dr. J. Downes for his review of the manuscript and many helpful suggestions.

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Letters to the Editor

Epidural Injection Does Cause an Increase in CSF Pressure

To the Editor:

The question of why an epidural blood patch has a rapid response in relieving postspinal headache has caused much speculation (1-3). The letter from Carrie (3) contends that the rapid relief is the result of the injected volume of blood raising the pressure in the epidural and spinal subarachnoid spaces so that cerebrospinal fluid (CSF) is forced back inside the cranium, cushioning the brain. We agree with this contention and support it with the following case report data.

A 74-yr-old, 70-kg man underwent a descending thoracic aortic aneurysm repair. The anesthesia consisted of a general anesthetic supplemented by a lidocaine epidural anesthetic converted to a continuous fentanyl and bupivacaine infusion for postoperative pain management. The epidural catheter was placed in the second to third lumbar interspace. To enhance spinal cord protection, a second catheter was placed in the lumbar subarachnoid space two levels below the lumbar epidural catheter. The CSF pressure was measured and CSF was withdrawn at the time of aortic cross-clamping to reduce the subarachnoid pressure and improve spinal cord perfusion. Withdrawing 20 mL of CSF reduced the CSF pressure from 17 to 7 mm Hg. It was noted that a bolus injection of 10 mL of 1.5% lidocaine with 1:200,000 epinephrine into the epidural space transiently increased the CSF pressure by 12 mm Hg for 1-2 min (Figure 1). This was a repeatable phenomenon. There was no change in systemic arterial blood pressure, pulmonary artery pressure, or central venous pressure at this time.

With an epidural blood patch, coagulation could occur

during these few minutes, and therefore the CSF pressure increase may be maintained (2).

We believe that this may answer the question of why an epidural blood patch relieves postspinal headache immediately.

Mike Ramsay, MD
Clayton Roberts, MD
Department of Anesthesiology
Baylor University Medical Center
3500 Gaston Avenue
Dallas, TX 75246

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A Potential Complication of the Patil-Syracuse Endoscopy Mask

To the Editor:

Fiberoptic endoscopy, along with various airway devices developed to facilitate tracheal intubation, has become increasingly popular in the management of the difficult airway (1). One such aid, the Patil-Syracuse mask (Figure 1), allows uninterrupted general anesthesia and ventilation while performing endoscopy for endotracheal intubation (2). The silicone diaphragm permits passage of a fibroscope together with the endotracheal tube (ETT) through the port without air leak (Figure 1).

We describe a case of a ruptured diaphragm that represented a potentially serious complication of this endoscopy mask.

A 32-yr-old, ASA physical status II man was scheduled for eye surgery with general endotracheal anesthesia. Review of a previous general anesthetic record revealed an unsuspected difficult tracheal intubation but easy ventilation via a mask. We elected to perform an "asleep" fiberoptic intubation with the Patil-Syracuse mask and an endoscopic airway. A 7.5-mm ETT, the silicone diaphragm, and the fibroscope were lubricated. The fibroscope was inserted through the silicone diaphragm and airway and directed into the trachea. The ETT was then gently passed through the diaphragm and advanced over the fibroscope. After raising the mask to further advance the ETT under direct vision, we discovered a remnant of the silicone diaphragm that was encircling the fibroscope and being advanced toward the airway by the aftercoming ETT (Fig-

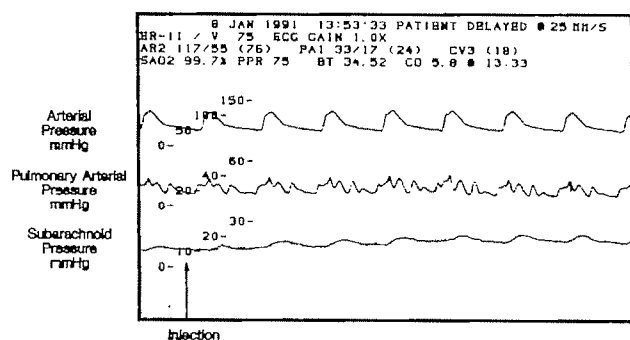


Figure 1. Radial artery, pulmonary artery, and subarachnoid pressure waveforms. Arrow represents injection of 10 mL of 1.5% xylocaine into the epidural space. Note increase in cerebrospinal fluid pressure from 10 to 22 mm Hg.

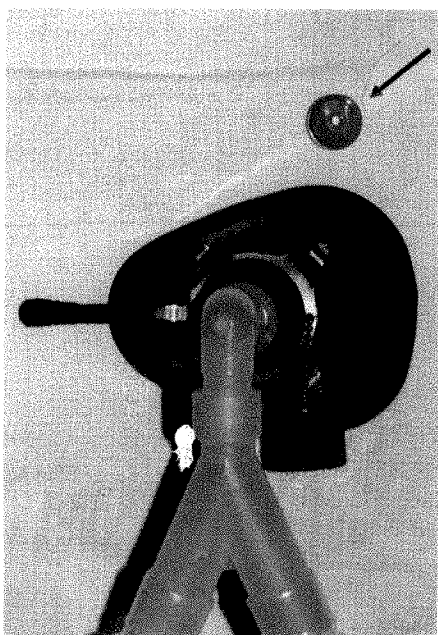


Figure 1. Patil-Syracuse mask (Anesthesia Associates, Inc.) with ruptured diaphragm and intact diaphragm (arrow) above.

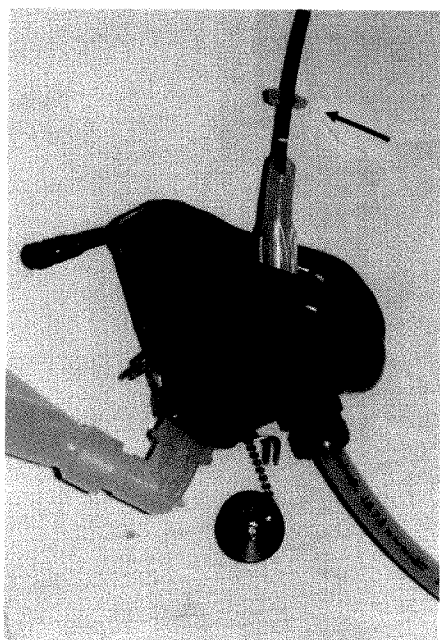


Figure 2. Displaced diaphragm remnant (arrow) encircling fiberoptic scope.

ure 2). The diaphragm ring was cut and removed from the fiberoptic scope with a subsequent, uneventful intubation.

Rupture of a Patil-Syracuse endoscopy mask's unlubricated diaphragm has been described previously (3,4). Despite lubrication as recommended by Zornow and Mitchell (3), the diaphragm in our case was ruptured without undue force. Although the manufacturer reports the recent production of a new, more durable diaphragm, the existing

diaphragms remain in supply and represent a foreign body hazard. When using the Patil-Syracuse mask, a generous lubrication of the fiberoptic and ETT and use of the more durable diaphragm appear to be warranted. Before guiding the ETT into the trachea, the integrity of the diaphragm should be assured.

Patrick H. Waring, MD
H. Ronald Vinik, MD
Department of Anesthesiology
University of Alabama
845 Jefferson Tower
619 South 19th Street
Birmingham, AL 35233-4696

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Neuromuscular "Block" Not "Blockade"

To the Editor:

Recent anesthesia literature increasingly uses the word "blockade" instead of "block" in neuromuscular pharmacology. The three-lettered suffix, *ade*, is unjustifiable.

The *Webster's New World Dictionary of the American Language* (Simon and Schuster) defines *blockade* as "a shutting off of a port or region of a belligerent state by. . . ." Other uses of the word share the connotation of a hostile military or police action. *Block*, on the other hand, is defined as "to impede the passage of progress of," etc.

Dorland's Illustrated Medical Dictionary (Saunders) defines *blockade* as "1. . . . phagocytosis . . . 2. . . . enzymatic actions. 3. the prevention of the effects of certain drugs by an agent, as the effect of nalorphine on heroin action." *Block* is defined as "1. any obstruction or stoppage. 2. a term introduced by Ramanes to express the obstruction of the passage of muscular or nervous impulses. 3. regional anesthesia" Numerous other medical uses of *block* exist in nerve block, heart block, mental block, etc.

Both *block* and *blockade* can be used as either a noun or a verb. However, *blockade* is not the noun of *block*. *Blockage* is a noun used in the phrase "the blockage of. . . ."

In neuromuscular pharmacology, curariform drugs are not used as agents that prevent the effects of other drugs ("blockade"), but are drugs that obstruct the passage of nervous impulses to the muscle ("block"). Rather, anticholinesterases may prevent the effects of curariform drugs ("blockade"). Therefore, the use of *blockade* in place of *block* not only wastes the suffix, but also adds wrong connotations. Besides, those who use *blockade* as a noun still use *block* as a verb, and write "blocking," "blocked," and "blocker," rather than "blockading," "blockaded," and "blockader." To be grammatically correct, they should have

used "block" not "blockade" to begin with. The use of "blockade" in regional anesthesia would be even less justifiable.

Chingmuh Lee, MD
Department of Anesthesiology
Harbor-UCLA Medical Center
1000 West Carson Street
Torrance, CA 90509

Use of a "Loading Port" for Syringe Pumps

To the Editor:

This is a response to the letter by O'Flynn and Siler (1) regarding the use of a "loading port" for syringe pumps. I was interested to note that they have used the Bard Infus O.R. and Baxter Auto syringe pumps with success, and they say this probably can be adapted to other pumps.

I have been using a loading port and an Ohmeda 9000 syringe pump but have run into one problem should the syringe need refilling more than twice. The syringe begins to lose its lubricant and becomes so stiff as to activate the "occlusion alarm." This then necessitates the changing of the syringe after fully checking the intravenous lines, which can be difficult.

I have found it easy to change syringes using the loading port after the second change as a matter of policy.

N. H. Ashurst, MD
Pontefract General Infirmary
Friarwood Lane
Pontefract, West Yorkshire
WF8 1 PL United Kingdom

Reference

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Sevoflurane Breakdown in Soda Lime

To the Editor:

A recent article has what we believe to be some misleading data (1). Succinctly, this article looked at temperatures attained in soda lime in a conventional anesthesia circuit during isoflurane anesthesia in humans, and the absorption and possible degradation of both sevoflurane and isoflurane in a model anesthesia circuit. We encountered a major difficulty with the use of the term "degradation of sevoflurane," which appeared many times in this article. The questions we pose are: how did the authors' methods differentiate between degradation and absorption of sevoflurane and isoflurane? What were the degradation products? We have unpublished data using low-flow sevoflurane anesthesia in humans with soda lime CO₂ absorption indicating that there are very low levels of degradation products arising, but these have been identified only with a

combination of gas chromatographic and mass spectroscopic analyses. These techniques were not used in the study by Liu et al., rather a Rascal (which does not measure degradation products to our knowledge) was used. Thus, we question how the term "degradation" could be used throughout the article. In addition, it is unclear why CO₂ absorbant temperature results obtained from the patients studied did not equate with temperatures in the model system evaluating "degradation." Indeed, the average highest temperature in the patient low-flow system was 43.5°C, yet studies in the model system used temperatures of 48.1, 48.7, and 49.4°C. Therefore, results in the model using these higher temperatures are not relevant to those occurring in the clinical situation because, as the authors infer, "breakdown" may be temperature-dependent.

Burnell R. Brown, Jr, MD, PhD, FFARCS
Edward J. Frink, Jr, MD
Department of Anesthesiology
The University of Arizona Health Sciences Center
Tucson, AZ 85724

Reference

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In Response:

Drs. Brown and Frink question whether we measured absorption or degradation of sevoflurane, and imply that the term "degradation" was inappropriate. There are three reasons why we used this term. First, Wallin et al. (1) and Hanaki et al. (2) demonstrated that sevoflurane is degraded by soda lime to fluoromethyl 2,2-difluoro-1-(trifluoromethyl) vinyl ether and fluoromethyl 2-methoxy-2,2-difluoro-1-(trifluoromethyl) ethyl ether. Indeed, Brown and Frink also note the formation of degradation products. Second, our group 3 (soda lime, CO₂) had a higher temperature in the absorbant than group 2 (soda lime, no CO₂). This increased temperature should have decreased absorption, but we observed the converse: a higher slope for group 3. Third, Figure 1 in our article gives rectilinear plots for data collected after 20 min. If absorption were a significant factor, these lines should have curved and approached a plateau as the absorption capacity of the soda lime became saturated. This reasoning extends with greater force to the data collected from Baralyme. Tanifuji et al. (3) found that absorption of sevoflurane by soda lime is a function of the silica binder. No such binder exists in Baralyme, yet we found that the disappearance of sevoflurane was three times as rapid with Baralyme as with soda lime.

All the above arguments point to degradation rather than absorption as the cause of the disappearing sevoflurane. The argument raised by Brown and Frink that only minute traces of degradation products arise in these circumstances ignores the possibility that the products derive from absorption or degradation by the soda lime.

Brown and Frink are curious about the trivial difference in absorbant temperature in the studies in anesthetized patients versus those in the model system. We delivered 200 mL/min of CO₂ into the model system. We think that this probably slightly exceeded the CO₂ production in the

patients studied, thereby producing a temperature of 48.1°C in group 3 as opposed to 43.5°C in the patients studied (both studies with soda lime; the still higher temperatures noted by Brown and Frink were obtained with Baralyme).

In summary, we continue to believe our data strongly support our conclusions that (a) degradation of sevoflurane by soda lime does occur and mandates a slightly increased input to sustain circuit concentration, but (b) the degradation is too small to materially affect the requirement for anesthetic delivery in clinical practice, even in a low-flow system.

Jin Liu, MD
Michael J. Laster, DVM
Edmond I. Eger II, MD
Shahram Taheri, BS
Department of Anesthesia
University of California, San Francisco
513 Parnassus Avenue
San Francisco, CA 94143-0454

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Metabolism of Sevoflurane

To the Editor:

A recent article by Yasuda et al. (1) comparing the kinetic characteristics of sevoflurane and isoflurane came to the conclusion "that the metabolism of sevoflurane did not differ from that estimated for isoflurane." Point of fact is that sevoflurane is biotransformed to a far greater extent in humans than is isoflurane in our experience. Under most circumstances, the technique to quantitate biotransformation should be to assay for metabolites. Sevoflurane is broken down in humans to a considerable extent into hexafluoroisopropanol and free fluoride ion, both of which can readily be detected. Although the mass balance technique described is sophisticated and mathematically intriguing, it seems to be inadequate to the task of determining biotransformation and could be quite misleading when it comes to statements concerning biotransformation.

Burnell R. Brown, Jr, MD, PhD, FFARCS
Edward J. Frink, Jr, MD
Department of Anesthesiology
University of Arizona Health Sciences Center
Tucson, AZ 85724

Reference

1. Yasuda N, Lockhart SH, Eger EI II, et al. Comparison of kinetics of sevoflurane and isoflurane in humans. *Anesth Analg* 1991;72:316-24.

In Response:

Drs. Brown and Frink correctly underscore the most important limitation of the mass balance technique. It can be too

insensitive to detect small differences in metabolism, and thus the conclusion that metabolism of sevoflurane does not differ from that of isoflurane might mislead the unwary reader. The following reasoning led us to pursue this less sensitive approach to a determination of metabolism. Mass balance has been used to assess the metabolism of enflurane, a compound that produces roughly the same amount of metabolites as sevoflurane (1). This technique revealed a significant difference from isoflurane, a difference greater than that suggested by assay of metabolites (2).

One could argue that dependence on assay of metabolites might lead to an underestimate of metabolism. Indeed, that also is what one might conclude from studies of mass balance (2) versus metabolite assay for halothane (3,4) and methoxyflurane (5): assay of metabolites appears to give a lower estimate of metabolism than the mass balance technique. The problem with the assay for metabolites is that the assay depends on access to the metabolites. If they are retained in inaccessible places (such as bone) or are eliminated by unmonitored routes (such as exhaled gases), the excreta examined may not reveal the true total metabolism.

We submit that the use of both approaches, mass balance and assay of metabolites may not give redundant information. The results of each may be combined usefully to understand the true extent of metabolism. Thus, we believe it reasonable to have pursued the estimate of metabolism of sevoflurane using mass balance.

Edmond I. Eger II, MD
University of California
Science-455 Box 0464
San Francisco, CA 94143-0464

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More About the Esophageal Detector

To the Editor:

I read Ian Smith's letter (1) in which he advocated the use of the "esophageal detector" with some concern. This device is supposed to *always immediately* determine endotracheal tube (ETT) position.

More than 2 yr ago, after reading the original description (2), I made a copy of the esophageal detector and used it in 18 patients. It failed to confirm proper ETT placement twice. This is not really surprising. In 1989 a similar failure of the device was reported (3) and even Wee, its designer, has reported 25 instances when it hasn't functioned ideally (4). I believe there is no *single* sign, test, or technology that will *always immediately* determine ETT position. This should be determined clinically using a combination of the tech-

niques reviewed by Birmingham et al. (5) and be confirmed using whatever technology is available.

In certain situations, CO₂ can be detected in the stomach (6,7) and although end-tidal CO₂ values of 6–10 mm Hg during cardiopulmonary resuscitation may correlate with hospital survival (8), they may not confirm the accurate placement of ETT. Similarly, some patients (especially pediatric patients, the morbidly obese, and those with lung disease) may have arterial desaturation after proper ETT placement. Certainly, premature removal of a properly placed ETT is as dangerous as unrecognized esophageal intubation.

Until that elusive single test of proper ETT placement is determined and/or capnography is available at every possible intubating location, we will still need to teach careful clinical evaluation of ETT placement, pay scrupulous attention to technique, maintain a high index of suspicion, and use all methods available to assess tube position (5).

Patrick J. Donahue, MD
Department of Anaesthesia
New England Deaconess Hospital
185 Pilgrim Road
Boston, MA 02215

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In Response:

I am pleased to hear that Dr. Donahue has been using the "esophageal detector device." Unfortunately, he omitted to provide full information on the two cases in which the device "failed to confirm proper ETT placement." Widespread trials and complete reporting of difficulties can assist in establishing the true role of this relatively new device.

In the published literature, the esophageal detector device has never been reported to give a false-negative result (i.e., to suggest that an ETT was in the trachea). The false-positive result reported by Calder et al. (1) resulted from the bevel of an unformed ETT impinging on the unsupported posterior tracheal wall. The authors recommend rotation of the tube and reapplication of the device after a positive result when this type of tube is used. In Wee's larger series (2), the 25 cases where the device did not "function ideally" all involved situations in which at least 20 mL of air could be withdrawn before encountering resistance. Wee states that this felt "quite different" from the resistance caused by esophageal intubation. He also recommends several measures (i.e., withdrawing the tube 0.5–1 cm, partial rotation) to be used in equivocal cases

before removing the tube. Wee's series involved use of the original esophageal detector device (which may prove to be of more value in equivocal tests), whereas Calder et al. used Nunn's modification (3). Unfortunately, Donahue does not state which form of the device he was using.

I would agree with Donahue that no single test should be relied upon to the exclusion of all other available methods. However, one of the major advantages of the esophageal detector device is that it can be present at *every* location at which endotracheal intubation is practiced, when other equipment may not be available. I would disagree with Donahue's statement that premature removal of a properly placed ETT is "as dangerous" as unrecognized esophageal intubation. Providing that intubation and ventilation via a mask were not unduly difficult, the safest practice should be to remove any ETT that is not definitely in the trachea. However, strict adherence to the protocol suggested by the original inventor of the esophageal detector device (2) should reduce the number of such occurrences to a minimum.

Ian Smith, FFARCS
Washington University
School of Medicine
Box 8054
660 South Euclid Avenue
St. Louis, MO 63110

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Management of a Systemic Carnitine Deficiency

To the Editor:

Rowe and Helander (1) reported the anesthetic management of a patient with systemic carnitine deficiency. Systemic carnitine deficiency is usually the result of an enzymatic defect in organic acid metabolism or fatty acid β -oxidation. Primary systemic carnitine deficiency owing to a transport defect is still very rare (2). The distinction between the two can be accomplished only by urinary organic acid analysis and appropriate enzymatic assays. These investigations should be performed in patients with serum carnitine deficiency before any elective surgical procedure. During metabolic decompensation, carnitine-deficient patients are "intoxicated" by the accumulated organic acids, some of which are able to inhibit fatty acid β -oxidation leading to decreased activity of pyruvate carboxylase (a gluconeogenic enzyme), whereas others do not interfere with fatty acid oxidation and gluconeogenesis but with ketone body utilization leading to metabolic acidosis with normo- or hyperglycemia. The immediate danger to carnitine-deficient patients during the early stages of metabolic decompensation is not hypoglycemia but mito-

chondrial acyl-coenzyme A accumulation with resultant neurologic and hepatic disturbances. Maintaining normal blood glucose levels with 5% dextrose would not prevent a catabolic state, and higher dextrose concentrations should be used with the possible addition of insulin.

Orly N. Elpeleg, MD
Metabolic Laboratory
Shaare-Zedek Medical Center
Jerusalem 91031, Israel

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In Response:

Doctor Elpeleg reemphasized a very important point in the care of patients with systemic carnitine deficiency: that when these patients get into a metabolic crisis, it is important not only to optimize their carnitine level but also to aggressively treat their hypoglycemia. Depending on the extent of their metabolic crisis, treatment may also be necessary for hypoprothrombinemia, hyperammonemia, acidosis, electrolyte disorders, or shock, as well as for other manifestations of the patient's hepatic failure and encephalopathy.

Primary serum carnitine deficiency is indeed extremely rare. According to Rebouche and Engel (1): "...[serum carnitine deficiency] could arise from one or more of the following: (1) a defect in carnitine biosynthesis; (2) abnormal renal handling of carnitine; (3) alterations in cellular mechanisms for carnitine transport, affecting uptake or release (or both) of carnitine from tissues; (4) excessive degradation of carnitine; or (5) defective intestinal absorption of carnitine."

Furthermore, there are more than 23 disorders of fatty and organic acid metabolism that can lead to secondary carnitine deficiency syndrome. Only through detailed analysis of a patient's lipid and organic acid metabolism can a diagnosis be assured. The anesthetic implications of secondary carnitine deficiency and myopathic carnitine deficiency are not the same as those discussed for systemic carnitine deficiency (2).

Richard Rowe, MD
Department of Anesthesiology
Children's Hospital
747 52nd Street
Oakland, CA 94609

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How Much Epinephrine in a Wash

To the Editor:

Mention of an "epinephrine wash" before spinal anesthesia (1) has prompted us to share the results of a study we did

Table 1. Comparison of Wash Methods

Group	Mean \pm SD (μ g)	Range (μ g)	Variability (%)
Two-milliliter syringes			
Wash A	81.5 \pm 7.7	62.6-94.2	9.4
Wash B	85.3 \pm 10.1	68.1-100.0	11.8
Tuberculin	103.1 \pm 2.7	95.8-106.6	2.7
Twenty-milliliter syringes			
Wash	122.3 \pm 14.6	101.5-169.5	11.9
Tuberculin	102.4 \pm 2.9	97.2-107.0	2.9

a few years ago. The aims were to determine how much epinephrine was added with a wash, its variability, and the effect of two wash techniques, and to compare these techniques with the addition of 0.1 mL of 1:1000 epinephrine using a 0.25-mL tuberculin syringe.

Five 2- and 20-mL glass syringes were weighed, five times each, before and after the wash or "injection" from the tuberculin syringe. For wash A, 0.1 mL of 1:1000 epinephrine was aspirated and the syringe was inverted to carry the plunger to the 2-mL mark and then reinverted to empty it; for wash B, 1 mL of the solution was aspirated, emptying it similarly. With the 20-mL syringes, a drop of epinephrine was aspirated and the plunger was drawn to the 20-mL mark and then emptied as before. The following formula was used to calculate the mass of epinephrine (M_e):

$$M_e = [(W_a - W_b)/D_e] \times C_e$$

where W_b and W_a are weights before and after the addition of epinephrine, C_e is the solution concentration, and D_e is its density.

Variability was significantly more ($P < 0.0001$) with the wash when compared with the tuberculin method for both wash techniques and syringe volumes (Table 1). Washes added less than 0.1 mg to the 2-mL syringes; this probably carries no risk other than a doubtful effect. By contrast, washes added up to 170 μ g to 20-mL syringes; maximum concentrations could reach 1:125,000 or 1:62,500 when diluting epinephrine with 20 or 10 mL of local anesthetic solution, respectively. These are dangerous concentrations that will not achieve a correspondingly more effective vasoconstriction. Thus epinephrine should be added with a tuberculin syringe (2).

Jorge Dagnino, MD
Guillermo Bugeño, MD
Departamento de Anestesiología
Universidad Católica de Chile
Santiago, Chile

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In Obstetrics: Keep the Water Colorless and Clear

To the Editor:

Recently, a trend was initiated by obstetricians and nurse midwives to relax the restriction of oral intake during parturition (1,2). However, it is well known that aspiration pneumonitis used to be the leading cause of maternal death from anesthesia (3,4). Only after becoming aware of the problems, selecting the proper anesthetic technique, and taking strict precautions against aspiration of gastric contents, including restriction of oral intake, has mortality decreased significantly in recent years (5,6). Is it safe to be so liberal with oral intake during labor as recommended by the authors of References 1 and 2? We measured the pH of the fluids commonly recommended for drinking during the course of labor. It is apparent from Table 1 that all tested fluids except water were acidic. Thus, drinking such *colored* fluids may increase the risk of aspiration of gastric contents by adding to its acidity and volume. Therefore, we recom-

Table 1. pH of Clear Fluids Recommended for Oral Intake During Labor

Fluid	pH
Tap water	7.20
Fruit juices ^a	
Apple	3.65
Grape	3.20
Cranberry ^b	2.70
Gatorade	
Orange	3.03
Lemonade	3.13

^aProduced by Campbell Soup Co., Camden, N.J.

^bProduced by Quaker Oats, Chicago, Ill.

mend that only water should be allowed during labor. If the course of parturition is prolonged, intravenous fluids containing dextrose should be administered to prevent maternal ketoacidosis. The mortality and morbidity from aspiration pneumonitis in the obstetric patient is real and not exaggerated. We believe that relaxation of current guidelines may be dangerous.

Ezzat Aboulzish, MD
Thomas Merriman, MD
Department of Anesthesiology
University of Texas at Houston
6431 Fannin, MSMB 5.020
Houston, TX 77030

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Continuous Spinal Anesthesia With Hyperbaric and Isobaric Bupivacaine

To the Editor:

We read with interest the clinical report on the combined use of hyperbaric and isobaric bupivacaine for continuous spinal anesthesia for labor, and subsequently for surgical delivery, in a patient with repaired congenital heart disease and severe kyphoscoliosis (1). We would like to make a few comments regarding the patient management as well as the techniques used.

Anesthetic solutions administered into the lumbar epidural space tend to spread more in the cranial than in the caudal direction. Despite the use of large doses, lumbar epidural block may fail to provide adequate analgesia over the sacral nerves in 10%-25% of patients (2-4). An epidural block with sensory loss from T-10 to L-2 is usually sufficient to relieve the discomfort of uterine contractions during the first stage of labor. Incomplete sacral nerve block may allow involuntary expulsive efforts, which will not interfere with the progress of labor. On the other hand, we do question whether speculation over the possibility of instrumental or cesarean delivery should justify the change from epidural to spinal. An epidural block, when properly managed, does not necessarily increase the incidence of forceps delivery (5-7); and, in case a forceps or cesarean delivery should be required, a subarachnoid block would be indicated only at that time.

Continuous spinal anesthesia can and has been used for labor, but must be at a concentration low enough to preserve the patient's motor functions. In the case described, however, both 0.75% hyperbaric and 0.5% isobaric bupivacaine were potent enough for surgical anesthesia with reduction of motor function. Therefore, it was not surprising that an "elective" cesarean section was required 16 h later because of failure to progress.

Our experience correlates with reports of others (8-12) that the major clinical virtue of isobaric spinal anesthetics is that the position or configuration of the patient has minimal effect on distribution of the anesthetic. Unless an excessive volume or dose is used, an isobaric spinal rarely produces a level of analgesia higher than the midthoracic area. The increased analgesia level on the right side of the patient cited was not likely to have been caused by the additional 1 mL of 0.5% isobaric bupivacaine. Although this solution is slightly hypobaric and may have "floated up" when the patient was in a 60° head-up position with left uterine displacement, it is hard to imagine that this isobaric solution reached an area that a hyperbaric solution could not, even after multiple position maneuvers. To insert a needle or catheter into epidural or subarachnoid space in a patient with severe kyphoscoliosis can be technically difficult. Nonetheless, once the needle or the catheter is properly placed, the spread or distribution of the anesthetics administered generally occurs without incident. This is especially true in subarachnoid block.

Finally, we fail to see the reason for leaving the spinal catheter in place for 12 h postoperatively after 0.4 mg of morphine was given. It is well documented that intrathecal administration of that dose of morphine will produce postoperative analgesia for more than 20 h (13,14).

Hwa-Kou King, M.D.
Daniel J. Wooten, M.D.
Department of Anesthesiology

Benedict S. Liao, M.D.
Department of Obstetrics and Gynecology
King/Drew Medical Center
Charles R. Drew University of Medicine and Science
12021 South Wilmington Avenue
Los Angeles, CA 90059

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In Response:

King et al. questioned "whether speculation over the possibility of instrumental or cesarean delivery should justify the change from epidural to spinal." We agree that "an epidural block with sensory loss from T-10 to L-2 is usually sufficient . . . during the first stage of labor." However, our patient had two conditions that placed her at increased risk for instrumental delivery. First, lumbar scoliosis may be associated with distortions in pelvic anatomy predisposing to cephalopelvic disproportion. Second, although this patient had undergone surgical repair of congenital heart disease, her status was far from normal. The driving force for her pulmonary circulation was the right atrial to pulmonary artery pressure gradient. The patient's cardiovascular system had not yet been stressed with the physiologic changes associated with labor and delivery. Significant increases in pulmonary vascular resistance or rapid decreases in systemic vascular resistance could have decreased pulmonary blood flow and cardiac output. The consequent cardiovascular instability would place both the

mother and the fetus at risk and increase the chance of urgent operative delivery. Our goal, therefore, was to provide an anesthetic technique that would allow us to (a) provide good labor analgesia, (b) abolish the urge to push should we need to do so, and (c) provide a titratable, predictable, and rapid anesthetic for urgent or emergent delivery. We hoped to avoid general anesthesia because (a) it was the patient's wish to be awake at delivery, (b) airway mishap and pulmonary aspiration of gastric contents still constitute the majority of maternal deaths due to anesthesia, and (c) positive pressure ventilation intraoperatively with increased intrathoracic pressures may have decreased venous return and pulmonary blood flow.

In response to the statement that "in case a forceps or cesarean delivery should be required, a subarachnoid block would be indicated only at that time," we believe that the risk of excessively high levels of anesthesia or total spinal after the superimposition of a spinal block on an existing epidural block in the parturient is unacceptably high. Furthermore, we wanted a technique that allowed a greater degree of control than a single bolus spinal would give us.

King et al. stated that "it was not surprising that an 'elective' cesarean section was required" because "both 0.75% hyperbaric and 0.5% isobaric bupivacaine were potent enough for surgical anesthesia with reduction of motor function." Although preservation of motor function may be important in the second stage of labor, several studies have demonstrated that spinal block up to the first thoracic (T₁) dermatome did not affect frequency, intensity, or tonus of uterine contractions provided hypotension was avoided (1). Our patient's progress was arrested in the first stage of labor despite oxytocin augmentation.

The spinal catheter was left in place for 24 h postoperatively (a) to provide anesthesia should any bleeding develop requiring reoperation and (b) to provide sympathetic block and vasodilation should cardiovascular decompensation occur with the resolution of the sympathectomy, return of vascular tone, and the dramatic increase in cardiac output in the immediate postpartum period.

Finally, we agree with all of Dr. King's comments regarding the effects of baricity and vertebral abnormalities on the spread of anesthesia. We, too, were surprised by our inability to achieve an adequate sensory level in both the epidural and continuous spinal techniques using relatively large doses of local anesthetics. We cannot explain why we were able to raise the level of sensory block on the right with the addition of an isobaric solution; we can only speculate on the possibilities and present the case to other experienced anesthesiologists for comments.

Deborah H. Moran, MD
Department of Anesthesia
Bowman Gray School of Medicine
Winston-Salem, NC 27104

Mark D. Johnson, MD
Department of Anesthesia
Brigham and Women's Hospital
Boston, MA 02115

Reference

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A Method of Introducing Aerosolized Medications Into the Anesthesia Circuit

To the Editor:

The availability of pressurized aerosol cannisters has facilitated endotracheal delivery of drugs. Occasionally, however, the adapter by which these units are connected to the anesthesia circuit is missing, causing delay of treatment until a new adapter is found. We describe a simple technique that permits fast and reliable administration of drugs from metered inhalation aerosol containers.

The cap of the gas sampling port on the elbow piece of the anesthesia circuit (e.g., Vital Signs) is removed, pierced in the center with an 18-gauge needle, and then replaced on the port. The stem of the cannister is then placed against the hole in the cap and pressed down firmly during inspiration (Figure 1). This system is assembled quickly and easily and is capable of delivering the measured amount of aerosolized drug into the endotracheal tube.

Keith J. Ruskin, MD
Levon Capan, MD
*Department of Anesthesiology
School of Medicine
NYU Medical Center
550 First Avenue
New York, NY 10016*

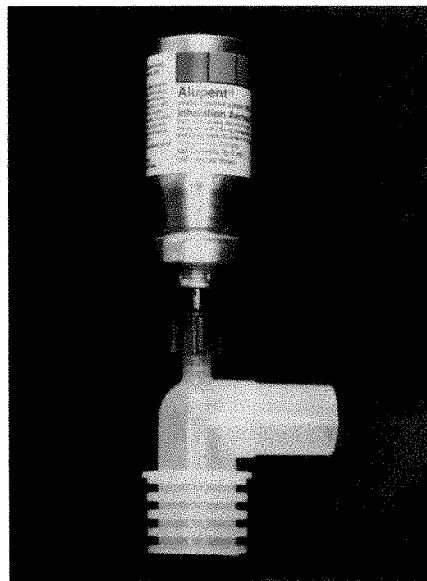


Figure 1

Book Reviews

Interdisciplinary Pain Management

International Anesthesiology Clinics,
Volume 29, No. 1

Philip W. Lebowitz, ed. Boston: Little Brown, 1991, 109 pp, \$38 single issue or \$81.00 subscription for four issues.

This is an excellent and concise review of selected topics in the area of pain management. The book covers a broad array of topics ranging from the psychologic aspects of pain to neurolytic blocks in cancer pain. Also included are reviews of pediatric pain management, low back pain, and reflex sympathetic dystrophy. This represents a rare book in the area that is to-the-point and easy to read in a short period of time. Clinicians not involved in pain management, as well as those with extensive experience, will find this book of value. It is, however, not meant to be nor will it suffice as a textbook of pain management.

The first chapter discusses one of the most important points to be made about this field: that the treatment of patients with chronic pain requires a multidisciplinary approach. No longer should solitary clinicians treat pain as a unimodal entity, but rather as a complex intertwining of psychologic, physical, and emotional factors. Pain clinics should have on hand the advice of a psychologist or psychiatrist, neurologist, neurosurgeon, occupational therapist, physical therapist, and anesthesiologist. The advantages of using the multidisciplinary approach in relation to outcome are discussed. Practical problems with billing and reimbursement are also addressed.

The chapter on the psychologic aspects of pain provides the anesthesiologist with several models with which to view a patient's pain "ordeal." This information is often overlooked by anesthesiologists too firmly grounded in the practice of physical medicine.

The chapter on pediatric pain management is noteworthy as it points out once again that children have real pain, which deserves to be treated with appropriate drug doses, and that it is safe to do so. The chapter addresses issues such as treating brief acute pain for invasive procedures and supplies several useful tables that contain dosages of opioid and nonsteroidal antiinflammatory drugs. The authors conclude that "to improve the treatment of pediatric pain, the attitudes of doctors, nurses and parents must change." This should be understood by the reader of this chapter if nothing else.

A brief chapter on chronic benign orofacial pain and dysfunction is essentially a concise review on temporomandibular joint disorders. Included is an outline of a clinical approach to evaluating such disorders and a summary of possible treatments of which "counseling remains of cardinal importance."

The current concepts on the treatment of low back pain

are outlined in a chapter that mentions the importance of conservative therapy, but concentrates on the anesthesiologists' major role in the treatment of low back pain—i.e., the epidural steroid injection. The reasons for why, when, and to whom epidural steroid injections should be administered are discussed as are the current controversies and complications that may occur.

In summary, this monograph nicely reviews a number of topics in multidisciplinary pain management. It is not a synopsis of anesthesia pain practice by any means. However, it should suffice to review the major areas of pain management for the general clinician not involved in this field. The book is also useful for those practitioners experienced in pain management who just want to read quickly through an updated review.

Alan Kestenbaum, MD

John J. Savarese, MD

*The New York Hospital-Cornell University Medical Center
New York, New York*

Anesthesiology and Pain Management

T. H. Stanley, M. A. Ashburn, and P. G. Fine, eds.
Boston: Kluwer Academic Publishers, 1991, 384 pp, \$130.50.

The editors of this book are drawn from the University of Utah Medical School in Salt Lake City, and the contents represent the proceedings of their 36th Annual Post Graduate Course in Anesthesiology. Although the book does not attempt to review all of the latest aspects of acute and chronic pain management, the thrust is in terms of a summary of the salient aspects of basic science and clinical treatments as they relate to the practice of anesthesia. The role of the anesthesiologist is introduced by a comprehensive description of the history of pain management by John Bonica and, in a subsequent chapter, the putative role this discipline should follow in the future. These are extremely informative and provide a valuable reference to both lay people and professionals having an interest in the scope of pain management.

The book receives its basic science foundations in five very succinct chapters by Drs. Yaksh and Basbaum who explore central and peripheral mechanisms underlying the neurophysiology, neuropharmacology, and humoral aspects of nociception. Although it might have helped the reader had the book been divided into two parts, the first 12 chapters are in fact devoted to the elemental basic and clinical knowledge necessary for an understanding of pain management. In this refrain, three excellent chapters by Dr.

Michael Cousins explore the role of the sympathetic nervous system in the production of pain, the clinical application of spinal opioids in acute and chronic pain, and the current role of neurolytic and neuroablative procedures in the control of pain. These chapters are completed by a useful review of local anesthetics, the place for regional anesthesia in the management of postoperative pain, and differential neural blockade by the late Dr. Benjamin Covino.

Although the book deals with acute and chronic pain, it places the responsibility for acute and postoperative pain directly with the anesthesiologist. No less than 11 chapters are devoted to this purpose. Comprehensive chapters on the assessment and clinical applications of acute pain, the methods of acute pain control, and how to develop an acute pain service are described by Dr. Brian Reddy; and the historical development, current use, and future place among other forms of pain management are discussed by Dr. Paul White. Acute pain control in children is discussed albeit briefly, and an interesting chapter reviews the place for controlled-release morphine in management of pain after surgery.

The last eight chapters focus on a discussion of chronic pain management including the interdisciplinary model, chronic pain in children, and two excellent chapters in which Kathleen Foley discusses the therapeutic strategies and role of adjuvant drugs and anesthetic blocks in the management of patients with pain and cancer.

As stated by the editors, the purposes of the textbook are to (a) "act as a reference for the anesthesiologist attending the meeting" and (b) "serve as a vehicle to bring many of the latest concepts in anesthesiology to others within a short time of the formal presentation." Certainly both purposes are met, although at some cost. For a proceedings, the book is extremely expensive and its price will deter many from its purchase simply because much of the material is available in other diverse references. It does, however, accomplish the objective of providing the entire subject within one set of covers. Another casualty of the speed with which this book has appeared is the inability of the proofreader to capture all the typos that have escaped both the authors and editors, such that there is an error rate of almost two for every three pages. Another shortcoming, probably for the same reason, is the fact that the book lacks an index. The book is, however, unique in being probably the first to identify a comprehensive role of pain management with anesthesiology and as such it will be useful for hospital administrators, health care planners, and departmental libraries. The book is obviously of interest to those who are involved in the treatment of acute and chronic pain and could serve as a window for those residents in anesthesiology who might be contemplating a career in anesthesiology pain management.

M. Stanton-Hicks, MD, MB, BS, FC ANESTH
Cleveland Clinic Foundation
Cleveland, Ohio

Problems in Respiratory Care: Clinical Applications of Hyperbaric Oxygen

R. E. Moon and E. M. Camporesi, eds. Philadelphia: Lippincott, 1991, 272 pp, \$27.00.

This book is a brief collection of chapters written by individual authors. Topics include the physiology and toxicity of oxygen, operational aspects of both multiplace and monoplace chambers, treatment of gas poisonings and gas bubble disease, and the field management of injured divers. The monograph ends with a brief chapter on sources of information in this unique field of medicine.

The preface points out that little has been written on the practical and technical aspects of hyperbaric therapy; the limited availability of facilities and training in this field make a monograph on this subject highly desirable. This monograph, however, falls somewhat short of its goal. Although there are a few good chapters, the book has no consistent theme. For example, the title suggests the book covers clinical applications, but only two such applications (CO poisoning and gas bubble disease) are discussed in any detail. Only three of the nine chapters have anything to do with the purpose of the book stated in the preface—"... practical aspects of hyperbaric care." Although the reviews on oxygen physiology and toxicity are adequate and fairly well referenced, they seem a bit out of place in a monograph on practical aspects (or clinical applications). The section on oxygen toxicity management would have been better placed in the oxygen toxicity chapter, as the discussed management is not unique to multiplace chambers. The chapter on monoplace chambers is outstanding and contains much useful practical information. The chapter on gas poisonings, although well written, organized, and referenced, also seems a bit out of place for this book, especially when discussing poisonings (HCN and H₂S) in which there is only a conjectural role for hyperbaric therapy.

The chapter on gas bubble disease is well written and organized. However, as altitude decompression sickness has both a different presentation and management, it would have been useful to address this area in more detail. Consolidation of both decompression sickness and arterial gas embolism into a single entity (decompression illness) because of the commonality of therapy has not received universal recognition and should not be listed as "preferred." Although the difficulty of separating decompression sickness from arterial gas embolism and their frequent coexistence is real, should therapy dictate diagnosis? It is usually the other way around!

The chapter on field management was disappointing. It is full of jargon, is poorly organized, concentrates on commercial saturation diving accidents and equipment for unspecified reasons, and is replete with nonrelevant figures, lists of supplies, and case reports. Surprisingly, this chapter contains almost nothing on the field management of diving accidents, or on the transport and transfer of injured divers—a vital concern to the predefinitive care in diving accidents. The final chapter in this book will be useful to newcomers in the field in finding the often obscure sources of information dealing with hyperbaric physiology and medicine.

There are a few topics falling under the heading of "practical aspects" that pop up frequently, are occasionally difficult, and would have been useful to include in such a monograph. How does one manage the claustrophobic patient? What are the most effective ways of dealing with aural barotrauma in the chamber? What about the conduct of CPR in the chamber? Should the chamber be decompressed for defibrillation? Finally, because of the recognized deficiency of well-controlled studies establishing the efficacy of hyperbaric oxygen in many of its indications, a chapter dealing with the design and conduct of clinical trials would be most welcome. How does one randomize? Is there an effective placebo? How is informed consent obtained? What questions need answering? A thoughtful discussion along these lines may help many hyperbaric practitioners contribute to the growing field of hyperbaric medicine. Perhaps then we can read less of how "Duke does it" and more of what are the most effective procedures and equipment.

Roderic G. Eckenhoff, MD
University of Pennsylvania
Philadelphia, Pennsylvania

Books Received

Receipt of the books listed below is acknowledged. Selected books from this list will be reviewed in future issues of the Journal.

The Journal solicits reviews of new books from its readers. If you wish to submit a review, before proceeding please send a letter of intent, identifying the book in question, to Dr. Norig Ellison, Department of Anesthesia, Hospital of the University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104. The Journal reserves the right of final decision on publication.

Fragen RJ, ed. *Drug Infusions in Anesthesiology*. New York: Raven Press, 1991, 340 pp, \$82.00.

Kaplan JA, ed. *Thoracic Anesthesia*. 2nd ed. New York: Churchill Livingstone, 1991, 769 pp, \$94.95.

Kaplan JA, ed. *Vascular Anesthesia*. New York: Churchill Livingstone, 1991, 717 pp, \$94.95.

Stoelting RK. *Pharmacology and Physiology in Anesthetic Practice*. 2nd ed. Philadelphia: J.B. Lippincott, 1991, 896 pp, \$89.50.

Zaloga GP. *The Critical Care Drug Handbook*. St. Louis: Mosby Year Book, 1991, 537 pp, \$24.95.

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The Logical Choice



Crucial Parameters in Selecting a Neuromuscular Blocking Agent

	Norcuron® (vecuronium bromide) for injection	Atracurium besylate
HEMODYNAMICS	No significant variations in blood pressure, cardiac output, or systemic vascular resistance. ¹	Statistically significant variations in blood pressure, cardiac output, and systemic vascular resistance. ¹ ($P < .05$)
HISTAMINE	Available clinical experience indicates that reactions commonly associated with histamine release are unlikely to occur. ¹⁻⁴	Precautions advised for patients in whom substantial histamine release would be hazardous (eg, clinically significant cardiovascular disease, asthma) ⁵
RECOVERY To 25% of control To 95% of control	25–45 min ³ 45–65 min ³	35–45 min ⁵ 60–70 min ⁵
DOSING FLEXIBILITY	The initial recommended dose is 0.08–0.1 mg/kg. Dose can be increased up to 0.28 mg/kg for long cases without significant histamine release or related cardiovascular side effects. ^{1,3,4}	Initial recommended dose is 0.4–0.5 mg/kg. A moderate histamine release and significant falls in blood pressure have been seen following a dose of 0.5 mg/kg ($P < .05$) and 0.6 mg/kg. ^{2,5,6}
STORAGE & SHELF LIFE	2-year shelf life in lyophilized form at room temperature. [†] Can be reconstituted with various IV solutions including Lactated Ringers. [‡]	2-year shelf life under constant refrigeration. [†] Upon removal from refrigeration to room temperature storage, use within 14 days even if rerefrigerated. ⁵

*Dose of atracurium above 0.5 mg/kg is not recommended.

‡Storage after reconstitution varies with solution. See package insert.

†As originally supplied by the respective manufacturers.

Norcuron®

(vecuronium bromide) for injection

The Logical Choice for Neuromuscular Blockade

See following page for brief summary of prescribing information.



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NEW JERSEY 07052

Norcuron®

(vecuronium bromide) for injection

Before prescribing, please consult complete product information, a summary of which follows:

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

CONTRAINDICATIONS: Norcuron® is contraindicated in patients known to have a hypersensitivity to it. **WARNINGS:** NORCURON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.

PRECAUTIONS: General: Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are unlikely to occur.

Renal Failure: Norcuron® is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore dosage should not be increased.

Hepatic Disease: Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® metabolism and excretion. Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, in rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness that may be first noted during attempts to wean patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. Continuous infusion or intermittent bolus dosing to support mechanical ventilation has not been studied sufficiently to support dosage recommendations.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTENT EXCESS DOSING.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron®.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron®, the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes. The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents act in the same fashion as does Norcuron®, therefore these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics with Norcuron® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium.

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate.

Other: Experience concerning injection of quinine during recovery from use of other muscle relaxants suggest that recurrent paralysis may occur. This possibility must also be considered for Norcuron®. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance the neuromuscular blockade.

Drug/Laboratory Test Interactions: None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron®. Norcuron® should be given to a pregnant woman only if clearly needed.

Pediatric Use: Infants under 1 year of age but older than 7 weeks, also tested under halothane anesthesia, are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. Information presently available does not permit recommendations for usage in neonates.

ADVERSE REACTIONS: Norcuron® was well tolerated and produced no adverse reactions during extensive clinical trials. The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action of Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See OVERDOSAGE for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit. (See PRECAUTIONS).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in very rare instances.

OVERDOSAGE: The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances, the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION: Before prescribing, please consult complete product information. Norcuron® (vecuronium bromide) for injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile

anesthetics and by prior use of succinylcholine (see PRECAUTIONS/Drug Interactions). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₅₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalational anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses. Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained.

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (See PRECAUTIONS).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90% suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of non-depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose.

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL*	0.2 mg/mL†
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

*10 mg of Norcuron® in 100 mL solution

†20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

NORCURON® INFUSION RATE — mL/MIN

Amount of Drug µg/kg/min	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Dosage in Children: Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults. Infants under one year of age but older than 7 weeks are moderately more sensitive to Norcuron® on a mg/kg basis than adults and take about 1½ times as long to recover. See also subsection of PRECAUTIONS titled Pediatric Use. Information presently available does not permit recommendation on use in neonates (see PRECAUTIONS). There are insufficient data concerning continuous infusion of vecuronium in children, therefore, no dosing recommendation can be made.

COMPATIBILITY: Norcuron® is compatible in solution with:

0.9% NaCl solution
5% glucose in water
Sterile water for injection
5% glucose in saline
Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE: 15-30°C (59-86°F). Protect from light.

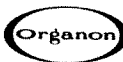
AFTER RECONSTITUTION:

- When reconstituted with supplied bacteriostatic water for injection, CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.
- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

REV. 3-89

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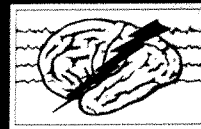
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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY THE B.B. SANKEY ANESTHESIA ADVANCEMENT AWARD

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Needles: A Sticky Situation for U.S. Healthcare.

Healthcare workers in America are facing an epidemic problem – needle sticks. Each year thousands of healthcare workers are accidentally stuck in hospitals, nursing homes, clinics and in general practice. These needle sticks can lead to very serious infections, with at least 20 percent pathogens having been identified as transmitted in this way.

In fact, the New England Journal of Medicine reported in its August 4th issue that as many as 12,000 healthcare providers contract hepatitis B each year. This is a large segment of the universe infected by accidental needle sticks. The seriousness can be seen in this statistic: 1

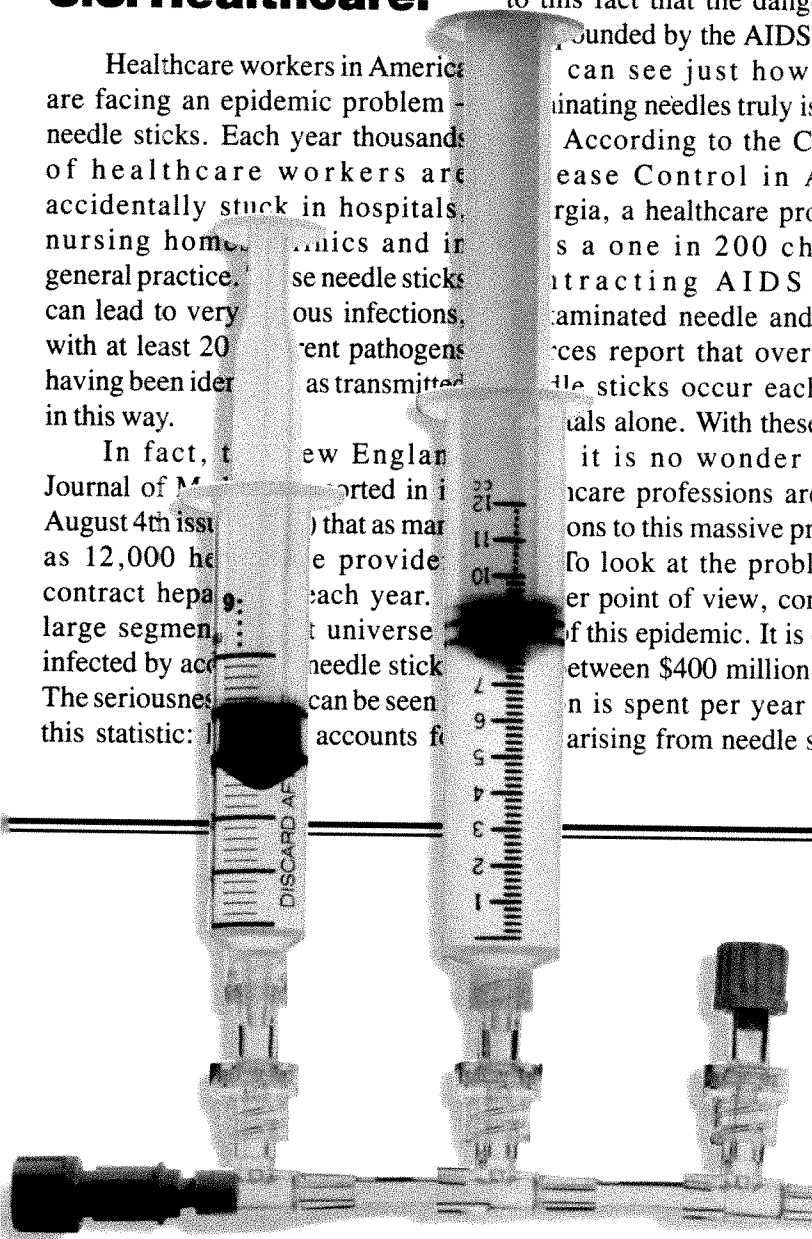
200 to 300 deaths a year to healthcare providers. And the number is growing every year. Add to this fact that the danger is now compounded by the AIDS virus and you can see just how critical eliminating needles truly is.

According to the Center for Disease Control in Atlanta, Georgia, a healthcare professional has a one in 200 chance of contracting AIDS from a contaminated needle and industry sources report that over 800,000 needle sticks occur each year in hospitals alone. With these kinds of statistics it is no wonder that the healthcare professions are seeking solutions to this massive problem. To look at the problem from another point of view, consider the scope of this epidemic. It is estimated that between \$400 million and \$1.0 billion is spent per year in direct costs arising from needle sticks and

this range does not include treatment or loss of work. In other words, aside from the human suffering associated with the infamous needle stick, the pocket book is infected, too.

One of the solutions to this huge problem facing the healthcare field today is the reduction of the total number of needles used in practice. One example of how the demand for needles can be reduced is the utilization of I.V. sets that provide luer connections which do not require needles.

With more than an estimated 1-million needle sticks per year, the situation is getting worse, not better. Until a solution is found, the American healthcare system will be under siege from the needle. What was once designed to deliver healing is now dealing misery – the needle: a sticky situation the U.S. healthcare profession must face.



When it comes to anesthesia sets, there is an innovative idea that could simplify your drug administration. Introducing the Quest "No-Needles" Anesthesia Sets.

Simply and safely luer lock your syringes or I.V. lines directly to our unique sets and administer medications as needed.

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No stopcocks to

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No Retrograding.
No Kidding.**

fumble with. No retrograding to foul your delivery. No need for repeated connects and disconnects. Not only does our "No-Needles" product line make great sense for the OR, but in ICU and CCU as well.

So if you're ready to say no to the needle, say yes to Quest. Quest Medical's "No Needles" Anesthesia Sets. Fax us today on your letterhead for a free sample. That fax number is 214-387-0501. Or call us toll-free at 1-800-527-0226. (In Texas call collect 214-387-2740).

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Cardiac Anesthesiologists

Cardiac and general anesthesiologists needed to join our team of 25 MDs, over 30 CRNAs and over 30 residents at Albany Medical College. Interest in teaching and research is highly desirable. The Albany Medical Center is a 660-bed, tertiary care facility with 20 newly renovated OR suites equipped with state-of-the-art instrumentation. Well established cardiac surgery program provides treatment for 1300 patients annually.

Benefits package includes generous leave time, health and dental plan, malpractice and life insurance. Interested applicants should send CV and 3 references to:

**Philip D. Lumb, MB, BS
Professor and Chairman
Albany Medical College
Dept of Anesthesiology
Mail Code A-131
Albany, NY 12208**

EEO/AA Employer M/F/H



ALBANY MEDICAL CENTER

FELLOWSHIP IN CRITICAL CARE HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA

Applications are solicited for a one year Critical Care Fellowship beginning in July 1992. Clinical training will include rotations on a combined surgery-anesthesia critical care team, a respiratory consultant service, a pediatric intensive care service, and a medical intensive care service. Research time will also be available. Please address correspondence with CV to:

**Ralph T. Geer, M.D.
Department of Anesthesia
Hospital of the University of Pennsylvania
3400 Spruce Street
Philadelphia, PA 19104-4283**

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Classified Advertising

FLORIDA

BC/BE anesthesiologist for expanding ambulatory group practice. Part time/full time with no nights, emergencies, OB, or weekends. Please reply to Box 621C/L.

621C/L

POSTDOCTORAL FELLOWSHIP

Background in clinical medicine or clinical research required for studies with patients with heart disease undergoing surgery. Cardiac function and ischemia assessed with ECG, Holter, and echocardiography monitoring. Working with cardiologists, epidemiologists, and anesthesiologists. Send CV and names of three references to Dennis T. Mangano, PhD, MD, Professor and Vice Chairman, Department of Anesthesia, University of California, San Francisco, 4150 Clement Street (129), San Francisco, CA 94121.

674E/D

OHIO

Anesthesiologist, University Hospitals. Must be at least board eligible. Equal Opportunity Affirmative Action Employer. Send curriculum vitae to Helmut F. Cascorbi, MD, PhD, Professor and Chairman, Department of Anesthesiology, University Hospitals of Cleveland, 2074 Abington Road, Cleveland, OH 44106.

701G/F

CARDIOVASCULAR FELLOWSHIP OPPORTUNITY

The Department of Anesthesiology at the University of New Mexico School of Medicine has openings at the CA-4 level for advanced training in Cardiovascular Anesthesiology beginning July 1992. The fellowship is a 2-year, comprehensive program designed to train the fellow for a career in cardiovascular anesthesiology. Research in cardiovascular physiology and anesthesia, provision of clinical care for complex adult and pediatric cases, participation in conferences, and teaching responsibilities are part of the fellowship experience. Interested individuals should contact Jorge Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico, 2211 Lomas Blvd. NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

730H/K

THE UNIVERSITY OF NEW MEXICO

Department of Anesthesiology has an immediate opening for a Veterans Administration Chief of Service for Anesthesia at

the New Mexico Regional Medical Facility (VA Hospital) in Albuquerque. Requirements include proven administrative, teaching, and leadership abilities, academic experience, and board certification. Appointment will be at the Associate Professor level. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

731H/K

THE UNIVERSITY OF NEW MEXICO

Department of Anesthesiology has faculty positions beginning July 1992 for the following: (1) Obstetrical Anesthesia at the Assistant, Associate, or Full Professor levels; (2) Critical Care Medicine at the Assistant or Associate Professor level. It is expected that candidates for CCM positions will have or be eligible for subspecialty certification. Faculty responsibilities include provision of clinical care, teaching, and research. Qualified candidates should send CV or contact Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

732H/K

THE UNIVERSITY OF NEW MEXICO

Department of Anesthesiology has faculty positions at the Instructor, Assistant Professor, and Associate Professor levels beginning July 1992. Responsibilities include teaching of medical students and residents and the provision of clinical care in a busy tertiary referral center. Opportunities to pursue research interest will be provided. Experience in cardiac, obstetric, neurosurgical, and pediatric anesthesia is desirable. Qualified candidates should address inquiries to Jorge A. Estrin, MD, PhD, Professor and Chairman, Department of Anesthesiology, University of New Mexico School of Medicine, 2211 Lomas NE, Albuquerque, NM 87106; (505) 843-2610. The University of New Mexico is an Equal Opportunity, Affirmative Action Employer.

733H/K

PAIN MANAGEMENT FELLOWSHIP

Unique training opportunity for highly motivated, patient-oriented, anesthesiologist

to participate in strong clinical pain management program. Emphasis on comprehensive evaluation and the use of neural blockade in the treatment of acute, chronic, and cancer pain. Training in interventional pain management techniques including implantable drug delivery systems and CT-guided neurodestructive procedures.

Applicant must possess strong interest in regional anesthesia and desire one-on-one patient contact. No OR or OB anesthesia responsibilities. Applicant MUST be BC/BE in anesthesia before beginning training. Fellowship period—1 year. Interested applicants should send CV to Pain Consortium of Greater Kansas City, 11111 Nall #202, Leawood, KS 66221.

714H/A

OHIO

ANESTHESIOLOGIST—METROHEALTH MEDICAL CENTER. Must be at least board eligible. Equal Opportunity Affirmative Action Employer. Send curriculum vitae to Lee S. Shepard, MD, Director, Department of

CLASSIFIED ADS

Anesthesia and Analgesia makes available classified advertising space for those interested in obtaining positions or wishing to announce meetings, postgraduate courses, or other pertinent events. We require that all advertisements be relevant to the practice of anesthesia and analgesia, and we reserve the right to refuse advertisements that are not relevant.

Specifications. Ads should be typewritten on letterhead stationery; the text should be double-spaced, with the title or key phrase typed in capital letters. Enclose two photocopies with each ad. Display space (minimum 1/4 page) is available through Pharmaceutical Media, Inc., 440 Park Avenue South, 14th floor, New York, NY 10016, telephone: (212) 685-5010, FAX: (212) 685-6126.

Rates. Ads cost \$1.50 per word per insertion, with a minimum of 20 words. Abbreviations, dates, initials, post office box numbers, telephone numbers, years, and zip codes are considered one word each. There is an additional fee of \$18.00 per insertion for box number ads.*

Payment. Full payment or institutional purchase order must accompany the copy for each ad. Ads received without a check or purchase order will be returned. (Make checks payable to Elsevier Science Publishing Company, Inc.)

Deadline. Copy must be received 7 weeks before publication date (i.e., by January 1 for the March issue); multiple-insertion ads are welcome. Ads may run up to 6 months per purchase order/payment. Please specify in which issue(s) your advertisement is to appear.

Send all ad copy, payments, and correspondence to: *Anesthesia and Analgesia*, Classified Ads, Desk Editorial, Elsevier Science Publishing Co., Inc., 655 Avenue of the Americas, New York, NY 10010.

*When responding to a box number ad, include the box number on all correspondence.

Anesthesiology, MetroHealth Medical Center, 3395 Scranton Road, Cleveland, OH 44109.

727H/A

INDIANA

Faculty positions are available at all academic ranks for adult anesthesia. Positions include teaching and administrative responsibilities as well as opportunities to pursue research interests. Experience in pain management and organ transplantation is desirable. All candidates must be board certified or board eligible. Individuals appointed to the tenure track will be required to maintain an active and ongoing research program. Please send curriculum vitae to Robert K. Stoelting, Professor and Chairman, Department of Anesthesia, Indiana University School of Medicine, 1120 South Drive, Fessler Hall 204, Indianapolis, IN 46202-5115. Indiana is an Equal Opportunity Employer.

743I/K

CHAIRMAN, DEPARTMENT OF ANESTHESIOLOGY

The University of Texas Medical School at Houston is seeking candidates for Chairman of its Department of Anesthesiology. Interested applicants should send a copy of their curriculum vitae to Joseph N. Corriere, Jr., MD, Chairman, Anesthesiology Search Committee, 6431 Fannin, Suite 6018, Houston, TX 77030. The University of Texas is an Equal Opportunity Employer.

745I/K

NEW YORK

CA-3 and CA-4 positions at Memorial Sloan-Kettering Cancer Center beginning July 1992. Advanced clinical and clinician-investigator opportunities available in critical care medicine, pain management, and anesthesia for thoracic surgery. Send CV and summary of career goals to Roger S. Wilson, MD, Chairman, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

747I/K

ANESTHESIOLOGIST

Three-man anesthesia group affiliated with multispecialty group seeks fourth physician for burgeoning practice. Competitive compensation benefit package including incentives. For more information contact Physician Recruiter, 850 Ridge Lake Boulevard G02, Memphis, TN 38120; (901) 684-3423.

751I/B

BE/BC ANESTHESIOLOGIST

SW PA, 300-bed, modern community hospital to work with three MDs and CRNAs. Competitive starting salary with malpractice and BC/BS. No open heart, minimal OB, minimal neuro. Reply to Box 753I/L.

753I/L

UNIVERSITY OF CALIFORNIA, DAVIS

Four (4) faculty positions at the assistant/associate/full professor levels. Some of these may be in the Professor-in-Residence series which is academic requiring clinical or basic research. Some of these may be in the Professor of Clinical Anesthesiology series where advancement is based on (1) clinical expertise, (2) teaching effectiveness, and (3) clinical publications. One position requires experience in acute and cancer pain management. One position requires subspecialty training and experience in pediatric anesthesia including cardiac and pain control. One position requires subspecialty training and certification in critical care to join two other faculty covering ICU 2-3 months per year. The fourth position requires demonstrated clinical teaching and interest in clinical studies in any area of anesthesiology. Please send letter, curriculum vitae, and names/addresses of three references to John H. Eisele, Jr, MD, Professor and Chairman, Department of Anesthesiology, 2315 Stockton Boulevard, University of California, Davis, Medical Center, Sacramento, CA 95817. The University of California, Davis, Medical Center is an Equal Opportunity/AA Employer. Rank and salary are commensurate with experience and based on the UCD School of Medicine Faculty Compensation Plan. Must be board certified or board eligible in anesthesiology, and a California medical license is required. All applications received by November 30, 1991, will receive thorough consideration.

758I/K

KENTUCKY

Full-time anesthesiologist, BC or BE, to fill available position immediately. Excellent salary and benefits including 8 weeks vacation. Group consists of four MDAs and 12 CRNAs practicing in a 380-bed hospital in western Kentucky on the Ohio River and very near two beautiful lakes. Send CV to Anesthesiology of Paducah, P.S.C., 2610 Broadway, Paducah, KY 42001 or call for further information: (502) 442-8228.

760I/K

NEW YORK

The STONY BROOK UNIVERSITY MEDICAL CENTER has CA-1 and CA-2 positions available for highly qualified AMGs starting January 1992. Interested applicants should request applications from Paul J. Poppers, MD, Department of Anesthesiology, University Hospital at Stony Brook, Stony Brook, NY 11794-8480. (516) 444-2975.

764JK

BLACK HILLS SOUTH DAKOTA

Single Hospital Regional Medical Center needs one or two anesthesiologists now. Care team practice with CRNAs. All specialties except cardiac. Low-stress practice. Wonderful setting. Clean air. Low crime.

Details: Rapid City Anesthesia Services P.C., P.O. Box 1560, Rapid City, SD 57709 768J/T

DEPARTMENT OF ANESTHESIOLOGY

St. Louis University School of Medicine is seeking board-qualified or certified full time faculty to fill newly created positions to meet the needs of the expanding residency program and new expanding hospital facility. Training and interests in the subspecialty areas of pediatrics, cardiovascular, pain, and neuroanesthesia are desirable. These clinical/teacher positions will also promote academic interests and research development. Participation in the residency training program is essential. The university is committed to affirmative action. Inquiries should be directed to John F. Schweiss, MD, Chairman, Department of Anesthesiology, St. Louis University School of Medicine, 3635 Vista Avenue at Grand Boulevard, St. Louis, MO 63110-0250; telephone (314) 577-8750.

772J/C

MEDICAL DIRECTOR, PAIN MANAGEMENT CENTER UNIVERSITY OF NEBRASKA MEDICAL CENTER

Exciting opportunity for motivated, board certified/eligible anesthesiologist for faculty position, as the Medical Director of an established Pain Management Center. The Pain Management Center has an active and growing acute and chronic pain management program. Position involves direct clinical work with acute and chronic pain patients, supervision and teaching of residents and students, as well as opportunities for basic and/or clinical research and program development. Prerequisites include experience in acute and chronic pain medicine. Responsibilities include directorship of a multidisciplinary outpatient pain control center.

Position at the Assistant or Associate Professor level with competitive salary commensurate with experience and qualifications. Excellent and complete compensation package including bonus potential. Full academic participation, didactic and clinical teaching.

The University of Nebraska Medical Center is designated a Level I trauma center and has an active liver and bone marrow transplant program among other surgical clinical programs. The Leon S. McGold Library of Medicine is one of the designated Midcontinental Regional Medical Libraries in the U.S.

Send curriculum vitae and two letter reference by December 31, 1991 to E. F. Landers, MD, PhD, Chairman, Department of Anesthesiology, University of Nebraska Medical Center, 600 South 42 Omaha, NE 68198-4455. The University of Nebraska is an Affirmative Action Opportunity Employer.

DIRECTOR, PAIN MANAGEMENT
The Department of Anesthesiology
Oregon Health Sciences University

recruiting for a Director of our Pain Management Service. The Service encompasses management of acute and chronic pain, training of medical students, residents, and fellows, and research. The Service provides a multidisciplinary approach to pain control and has vigorous clinical psychology and neuroimplant components. Excellent interdisciplinary relationships exist with Neurosurgery, Orthopedics, and Surgical Oncology. Board eligibility in anesthesiology or equivalent certification plus training and/or experience in pain management are required. Research experience and evidence of productivity are desired. Academic rank for successful candidate will be determined by qualifications. Candidate must be eligible for Oregon medical license.

Please send curriculum vitae and names of three references to Wendell C. Stevens, MD, Department of Anesthesiology, OHSU, 3181 SW Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an Equal Opportunity/Affirmative Action Employer.

774J/L

ASSOCIATE IN PAIN MANAGEMENT OREGON HEALTH SCIENCES UNIVERSITY SCHOOL OF MEDICINE

The Department of Anesthesiology at the Oregon Health Sciences University School of Medicine is recruiting for a full-time faculty member at the assistant professor level. The successful recruit will have an academic appointment in the School of Medicine and will have teaching and research responsibilities in the Pain Management Center of our University Hospital. Candidates should have specific training (at least 3 months) in pain management and related research and should have experience in a multidisciplinary pain management center. Candidates should have an aptitude for research, demonstrated by primary authorship of peer-reviewed publications in the field of pain management and/or regional anesthesia. Ability to interact with basic and clinical scientists should be shown. Candidate should be certified by the American Board of Anesthesiology and have an Oregon medical license. Interested candidates should send their curriculum vitae and the name of three references to Wendell C. Stevens, MD, Department of Anesthesiology, Oregon Health Sciences University, 3181 SW Sam Jackson Park Road, Portland, OR 97201. The Oregon Health Sciences University is an Equal Opportunity/Affirmative Action Employer.

775J/L

ANSAS, LITTLE ROCK

Group of seven MDs and 10 CRNAs searching for one or two BC/BE anesthesiologists. Areas of anesthesia with some CRNA position. Opportunities available in Pain Management. 341-Bed hospital. Well-established group with equally shared call vacation benefits. Beautiful rolling hills and many outdoor recreational activities in area. Send CV to Garry Jones, MD,

Capitol Anesthesia Group, St 606, 500 South University, Little Rock, AR 72205.

777J/A

PEDIATRIC ANESTHESIOLOGY FACULTY

Section of Pediatric Anesthesiology at the University of Michigan Medical School is seeking an additional faculty member. The Section provides anesthesia for a surgical caseload of 6000 cases/year, 50% of which are outpatients. All pediatric surgical subspecialties are represented, with an active pediatric cardiac surgery program of over 500 cases/year. An expanding pediatric pain program is currently being developed. Candidates should be BE/BC with a fellowship in pediatric anesthesiology. Appointments can be from the Lecturer to the Professor level in either the clinical or academic track, depending on qualifications and experience. Resources are available for faculty to participate in clinical and laboratory research. Interested candidates should apply to Niall Wilton, MD, Chief, Section of Pediatric Anesthesiology, C-4139, Med Inn Bridge, Box 0800, University of Michigan Medical Center, Ann Arbor, MI 48109-0800 (FAX 313-936-9091). The University of Michigan is a nondiscriminatory, Affirmative Action/Equal Opportunity Employer.

778J/I

WASHINGTON, D.C.

Positions available immediately and during the next year for full-time BE/BC anesthesiologists to join a growing MD/CRNA practice. Large ambulatory and challenging tertiary care caseload including all specialties except pediatrics at university-affiliated hospital. Reasonable call schedule with competitive compensation package and partnership after 1 year. Send or fax CV to Barney S.H. Feinstein, MD, Chairman, Department of Anesthesia, Washington Hospital Center, 110 Irving Street, NW, Washington, DC 20010; Fax number (202) 877-5564 or call collect (202) 877-7500.

721H/A

AVAILABLE IMMEDIATELY

In the Greater Cleveland Area a position for an MD anesthesiologist with Fellowship and/or Pain Management. Department has a very rapidly growing Pain Management Center, wide variety of blocks and invasive procedures performed. Active ongoing research. Must be able to contribute significantly to the growth in this area, in addition to operating room duties. No OB or hearts. Excellent compensation and benefits leading to early partnership. If interested apply to Box 734HIKL with current CV.

734HIKL

ANESTHESIOLOGIST

Three-person board-certified group in MIDWEST seeks fourth; strong practice in regional anesthesia and acute and chronic pain management. Group conducts office interview of patients prior to surgery. Ex-

cellent comradery within and between group, medical staff, and hospital. Broad range of cases, no OB or open hearts. First year salaried followed by equal ownership position. Reply in confidence to Box 784K.

784K

ILLINOIS

Large, well-established, single-specialty group of anesthesiologists seeks additional BC/BE anesthesiologists. Challenging opportunity for those interested in a broad based practice. All surgical subspecialties represented with coverage at three hospitals and two day-surgery facilities. Excellent benefits with early partnership. Please send CV to Associated Anesthesiologists, S.C., 5401 North Knoxville, Suite #49, Peoria, IL 64614.

785K/F

PEDIATRIC ANESTHESIOLOGIST

Needed to join seven others. We are especially interested in candidates with expertise in pediatric cardiac anesthesia and/or pediatric critical care. We administer over 4500 pediatric anesthetics each year including 250 open heart procedures, major burns, spinal fusions, as well as renal, cardiac, and liver transplants. In the OR, we supervise anesthesia residents on the CA-2 and CA-3 level. In the ICU, we provide medical direction and concurrent care, supervising pediatric residents. Our 183-bed tertiary-care hospital is staffed by full-time faculty of the Temple University School of Medicine. Candidates with excellent credentials, BE/BC by the ABA (and preferably the ABP), and at least 12 months of subspecialty training in pediatric anesthesia and critical care are invited to apply. Please send CV and names of three references (with phone numbers) to David A. Lowe, Director, Department of Anesthesia and Critical Care, St. Christopher's Hospital for Children, Erie Avenue at Front Street, Philadelphia, PA 19134. EO/AA Employer.

786K

ANESTHESIOLOGIST—NORTHEASTERN PENNSYLVANIA

Immediate position available for full-time BC/BE anesthesiologist to join group of eight. Excellent salary leading to partnership. Full benefits. No neuro or open heart. Send curriculum vitae to Box 787K

787K

LOUISIANA STATE UNIVERSITY MEDICAL CENTER—SHREVEPORT

Faculty positions available for board certified/eligible anesthesiologists. Duties include patient care, resident and student teaching, supervision of CRNAs, research, and administrative responsibilities. Faculty rank and salary commensurate with experience. Please send curriculum vitae and names of three references to D. Richard Davis, II, MD, Associate Professor and Chairman, Department of Anesthesiology, LSU Medical Center-Shreveport, 1501 Kings Highway,

Shreveport, LA 71130-3932. We are an Equal Opportunity/Affirmative Action Employer.
788K/D

PARTNER SOUGHT!

BC/BE anesthesiologist needed for congenial practice in beautiful Berkshires, 3 hours from NYC and Boston. Practice with three CRNAs and other MD; no OB, no OH, no trauma. No in-house call. Starting salary about \$125K, plus benefits, commensurate with Board status and experience. Partnership after 6 months. Liberal vacation and free-time allows enjoyment of area's rich cultural, educational, and recreational resources. Position available now but will wait for "right" MD or DO. Send CV and letter to Harry Sernaker, MD; 153 Leona Drive, Pittsfield, MA 01201.

789K

The Pain Consortium of Greater Kansas City is seeking a BC/BE anesthesiologist to serve as Associate Clinical Director. An excellent career opportunity for a highly motivated individual who is interested in practicing full-time pain management with an innovative and busy pain management team. Excellent people skills and a desire for one-on-one patient contact is necessary. Above average general medical knowledge and ability in the use of neural blockade in the treatment of pain is a must. Willingness to participate in active clinical research and our fellowship training program is desirable. If you are a hard-working and quality-minded team player—this may be the job you've been looking for. Send your CV and three letters of recommendation to Steven D. Waldman, MD, Director, Pain Consortium of Greater Kansas City, 11111 Nall #202, Leawood, KS 66211.

790K/A

UNIVERSITY OF MIAMI—SCHOOL OF MEDICINE

Associate Professor Clinical Anesthesiology for university medical center. Clinical duties include functioning as Director of Liver Transplantation Anesthesiology program. Requires Florida medical license and certification or eligibility for certification by American Board of Anesthesiology. Duties include teaching medical students and resident physicians in clinical anesthesia and doing clinical research in immunological suppressing agents. Requires 1 year experience in organ transplantation and 2 additional years experience in liver transplantation anesthesiology subsequent to anesthesiology residency. Hours 8 AM to 5 PM, Monday-Friday (40 hours/week + minimum 4 hours/week on call and further time as required). Salary \$2200 to \$2900/week as warranted by experience. Apply by resume to Job Service of Florida, Mezzanine, 701 SW 27 Avenue, Miami, FL 33133, ref. J.O. #FL 0486234.

791K

NORTHERN NEW ENGLAND

Staff anesthesiologist, BC/BE for 194-bed VA Medical Center, fully integrated academic anesthesiology department of the Dartmouth-Hitchcock Medical Center and Dartmouth Medical School. Active teaching hospitals. Academic appointments and salary commensurate with experience. Part-time position a possibility. Good schools, cultural offerings, beautiful country environment, good skiing, excellent book store. 2.5 hours from Boston, Massachusetts; 1.5 hours from Burlington, Vermont. For further information, call Andrew Gettinger, MD, Chairman VA Anesthesia Search Committee, or D. David Glass, MD, Chairman, Department of Anesthesiology, 603-646-5922 (FAX: 603-646-8980). Or send CV to above at Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756. EOE/MF.

792K/A

PEDIATRIC ANESTHESIOLOGIST

The Nemours Children's Clinic, a pediatric tertiary-care subspecialty clinic, located on the St. Johns River in Jacksonville, Florida, is seeking a staff pediatric anesthesiologist. Nemours is a partner in a consortium, comprised of the new Children's Hospital, the University of Florida College of Medicine, and University Medical Center of Jacksonville, for the development of a Regional Pediatric Medical Center. In order to provide innovative services and additional patient care in the new Children's Hospital, Nemours is expanding its Department of Anesthesiology. Candidates must be BC/BE in anesthesiology. A pediatric anesthesiology fellowship or the equivalent in experience is preferred. The salary and fringe benefits for this position are paid by Nemours Children's Clinic as this is a nonsalaried, University of Florida College of Medicine Courtesy Clinical faculty appointment at the rank of Assistant Professor/Associate Professor. Proximity to First Coast beaches, cultural and recreational opportunities, and year-round mild climate, as well as an opportunity for professional growth and participation in research, make this a very desirable employment choice. The recruiting deadline is 12/15/91. Interested applicants should send CV to Dr. Richard Helfrich, Jr., Chairman, Search Committee, Nemours Children's Clinic, 807 Nira Street, Jacksonville, FL 32207, (904)390-3766. Affiliated with the University of Florida, an Equal Opportunity, Affirmative Action Employer.

793K

PENNSYLVANIA

Faculty position available at Wills Eye Hospital. Board certification or presently in the examination system required. The candidates should have interest and expertise in pediatric and neonatal anesthesia. The successful candidate will have a full-time faculty position in the Department of Anesthesiology of Thomas Jefferson University. This is an excellent opportunity for teach-

ing and research at one of the most prestigious ophthalmologic hospitals in the country. Thomas Jefferson University is an Affirmative Action/Equal Opportunity Employer. Send CV and references to Joseph L. Seltzer, MD, Professor and Chairman, Department of Anesthesiology, Thomas Jefferson University, 111 South 11th Street, Suite 6460 Gibbon, Philadelphia, PA 19107.
794K/.

CALIFORNIA

Practice opportunities for BE/BC anesthesiologists to share call in South Bay Area. Send CV to AAMG, 725 East Santa Clara Street, Suite 101, San Jose, CA 95112.

795K

FLORIDA

Academic anesthesiologist. Two Assistant Professor positions available for board-certified or board-eligible anesthesiologists. Specialty training or experience in obstetrical anesthesia or pain management preferred. Positions available January 2, 1992 or later. Application deadline is December 2, 1991. Send request for interview and CV to Robert E. Redfern, MD, Search Committee Chairman, Department of Anesthesiology, University Medical Center, 655 West 8th Street, Jacksonville, FL 32209. Equal Employment Opportunity/Affirmative Action Employer.

796K

ANESTHESIOLOGIST/CRNA: FLORIDA

Excellent starting opportunity, unexpected position available, October 1991. Growing 100-bed hospital in suburban community, 30 minutes north of Tampa Bay. Full partnership in 2 years. BE/BC. PO Box 1166, Dade City, FL 33525. (813) 788-0411, Ext. 2315 or (813) 782-0285.

797K

ANESTHESIA CRITICAL CARE FELLOWSHIP: NORTHWESTERN UNIVERSITY MEDICAL SCHOOL

Twelve-month ACGME-accredited Critical Care Fellowship position available for anesthesiology CA-4 (PGY V) candidates beginning July 1992 or January 1993. Clinical experience includes all aspects of critical care medicine in medical, neurosurgical, pediatric, surgical, and spinal cord ICUs. This fully accredited Critical Care Training Program has been functioning for over 10 years and is supervised by three full-time anesthesiology intensivists. Research opportunities available for those interested. Send inquiries and application request to Barry A. Shapiro, MD, Section of Respiratory and Critical Care Medicine, Department of Anesthesia, Northwestern University Medical School, 250 East Superior Street, Suite 678, Chicago, IL 60611.

798KL

ANESTHESIOLOGIST

Board certified/eligible to join expanding small group practice. Experienced in all

esthesia techniques including epidural block and pain management. No open heart or neurosurgery. Good opportunity or growth. Please send CV to Mount Vernon Anesthesia Associates, Box 391, Mount Vernon, OH 43050.

799K/A

OHIO

Anesthesiologist to join a professional corporation of 11 anesthesiologists and 40 CRNAs in a progressive, 500-bed hospital. Salaried position for day shift. No night call or holidays. Excellent financial compensation. Please reply with CV to Michael J. Hovan, MD, PhD, Chairman, Department of Anesthesia, Akron City Hospital, 525 East Market Street, Akron, OH 44309.

800KL

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